ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Nexavar 200 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 200 mg of sorafenib (as tosylate).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet (tablet).

Red, round, biconvex film-coated tablets, debossed with Bayer cross on one side and "200" on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Hepatocellular carcinoma

Nexavar is indicated for the treatment of hepatocellular carcinoma (see section 5.1).

Renal cell carcinoma

Nexavar 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.

Differentiated thyroid carcinoma

Nexavar is indicated for the treatment of patients with progressive, locally advanced or metastatic, differentiated (papillary/follicular/Hürthle cell) thyroid carcinoma, refractory to radioactive iodine.

4.2 Posology and method of administration

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

Posology

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

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

Posology adjustments

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

When dose reduction is necessary during the treatment of hepatocellular carcinoma (HCC) and advanced renal cell carcinoma (RCC), the Nexavar dose should be reduced to two tablets of 200 mg sorafenib once daily (see section 4.4).

When dose reduction is necessary during the treatment of differentiated thyroid carcinoma (DTC), the Nexavar dose should be reduced to 600 mg sorafenib daily in divided doses (two tablets of 200 mg and one tablet of 200 mg twelve hours apart).
If additional dose reduction is necessary, Nexavar may be reduced to 400 mg sorafenib daily in divided doses (two tablets of 200 mg twelve hours apart), and if necessary further reduced to one tablet of 200 mg once daily. After improvement of non-haematological adverse reactions, the dose of Nexavar may be increased.

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

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

Renal impairment
No dose adjustment is required in patients with mild, moderate or severe renal impairment. No data is available in patients requiring dialysis (see section 5.2).

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

Hepatic impairment
No dose adjustment is required in patients with Child Pugh A or B (mild to moderate) hepatic impairment. No data is available on patients with Child Pugh C (severe) hepatic impairment (see sections 4.4 and 5.2).

Method of administration

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

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Dermatological toxicities

Hand foot skin reaction (palmar-plantar erythrodysaesthesia) and rash represent the most common adverse drug reactions with sorafenib. Rash and hand foot skin reaction are usually CTC (Common Toxicity Criteria) Grade 1 and 2 and generally appear during the first six weeks of treatment with sorafenib. Management of dermatological toxicities may include topical therapies for symptomatic relief, temporary treatment interruption and/or dose modification of sorafenib, or in severe or persistent cases, permanent discontinuation of sorafenib (see section 4.8).

Hypertension

An increased incidence of arterial hypertension was observed in sorafenib-treated patients. Hypertension was usually mild to moderate, occurred early in the course of treatment, and was amenable to management with standard antihypertensive therapy. Blood pressure should be monitored regularly and treated, if required, in accordance with standard medical practice. In cases of severe or persistent hypertension, or hypertensive crisis despite institution of antihypertensive therapy, permanent discontinuation of sorafenib should be considered (see section 4.8).

Haemorrhage

An increased risk of bleeding may occur following sorafenib administration. If any bleeding event necessitates medical intervention it is recommended that permanent discontinuation of sorafenib should be considered (see section 4.8).

Cardiac ischaemia and/or infarction

In a randomised, placebo-controlled, double-blind study (study 1, see section 5.1) the incidence of treatment-emergent cardiac ischaemia/infarction events was higher in the sorafenib group (4.9 %) compared with the placebo group (0.4 %). In study 3 (see section 5.1) 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 section 4.8).

QT interval prolongation

Sorafenib has been shown to prolong the QT/QTc interval (see section 5.1), which may lead to an increased risk for ventricular arrhythmias. Use sorafenib with caution in patients who have, or may develop prolongation of QTc, such as patients with a congenital long QT syndrome, patients treated with a high cumulative dose of anthracycline therapy, patients taking certain anti-arrhythmic medicines or other medicinal products that lead to QT prolongation, and those with electrolyte disturbances such as hypokalaemia, hypocalcaemia, or hypomagnesaemia. When using sorafenib in these patients, periodic monitoring with on-treatment electrocardiograms and electrolytes (magnesium, potassium, calcium) should be considered.

Gastrointestinal perforation

Gastrointestinal perforation is an uncommon event and has been reported in less than 1% of patients taking sorafenib. In some cases this was not associated with apparent intra-abdominal tumour. Sorafenib therapy should be discontinued (see section 4.8).

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 sections 4.2 and 5.2).

Warfarin co-administration

Infrequent bleeding events or elevations in the International Normalised Ratio (INR) have been reported in some patients taking warfarin while on sorafenib therapy. Patients taking concomitant warfarin or phenprocoumon should be monitored regularly for changes in prothrombin time, INR or clinical bleeding episodes (see sections 4.5 and 4.8).

Wound healing complications

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

Elderly population

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

Drug-drug interactions

Caution is recommended when administering sorafenib with compounds that are metabolised/eliminated predominantly by the UGT1A1 (e.g. irinotecan) or UGT1A9 pathways (see section 4.5).

Caution is recommended when sorafenib is co-administered with docetaxel (see section 4.5).

Co-administration of neomycin or other antibiotics that cause major ecological disturbances of the gastrointestinal microflora may lead to a decrease in sorafenib bioavailability (see section 4.5). The risk of reduced plasma concentrations of sorafenib should be considered before starting a treatment course with antibiotics.

Higher mortality has been reported in patients with squamous cell carcinoma of the lung treated with sorafenib in combination with platinum-based chemotherapies. In two randomised trials investigating patients with Non-Small Cell Lung Cancer in the subgroup of patients with squamous cell carcinoma treated with sorafenib as add-on to paclitaxel/carboplatin, the HR for overall survival was found to be 1.81 (95% CI 1.19; 2.74) and as add-on to gemcitabine/cisplatin 1.22 (95% CI 0.82; 1.80). No single cause of death dominated, but higher incidence of respiratory failure, hemorrhages and infectious adverse events were observed in patients treated with sorafenib as add-on to platinum-based chemotherapies.

Disease specific warnings

Differentiated thyroid cancer (DTC)

Before initiating treatment, physicians are recommended to carefully evaluate the prognosis in the individual patient considering maximum lesion size (see section 5.1), symptoms related to the disease (see section 5.1) and progression rate.

Management of suspected adverse drug reactions may require temporary interruption or dose reduction of sorafenib therapy. In study 5 (see section 5.1), 37% of subjects had dose interruption and 35% had dose reduction already in cycle 1 of sorafenib treatment.

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

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

Hypocalcaemia in DTC
When using sorafenib in patients with DTC, close monitoring of blood calcium level is recommended. In clinical trials, hypocalcaemia was more frequent and more severe in patients with DTC, especially with a history of hypoparathyroidism, compared to patients with renal cell or hepatocellular carcinoma. Hypocalcaemia grade 3 and 4 occurred in 6.8% and 3.4% of sorafenib-treated patients with DTC (see section 4.8). Severe hypocalcaemia should be corrected to prevent complications such as QT-prolongation or torsade de pointes (see section QT prolongation).

TSH suppression in DTC
In study 5 (see section 5.1), increases in TSH levels above 0.5mU/L were observed in sorafenib treated patients. When using sorafenib in DTC patients, close monitoring of TSH level is recommended.

Renal cell carcinoma

High Risk Patients, according to MSKCC (Memorial Sloan Kettering Cancer Center) prognostic group, were not included in the phase III clinical study in renal cell carcinoma (see study 1 in section 5.1), and benefit-risk in these patients has not been evaluated.

4.5 Interaction with other medicinal products and other forms of interaction

Inducers of metabolic enzymes

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

CYP3A4 inhibitors

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

CYP2B6, CYP2C8 and CYP2C9 substrates

Sorafenib inhibited CYP2B6, CYP2C8 and CYP2C9 *in vitro* with similar potency. However, in clinical pharmacokinetic studies, concomitant administration of sorafenib 400 mg twice daily with cyclophosphamide, a CYP2B6 substrate, or paclitaxel, a CYP2C8 substrate, did not result in a clinically meaningful inhibition. These data suggest that sorafenib at the recommended dose of 400 mg twice daily may not be an *in vivo* inhibitor of CYP2B6 or CYP2C8.
Additionally, concomitant treatment with sorafenib and warfarin, a CYP2C9 substrate, did not result in changes in mean PT-INR compared to placebo. Thus, also the risk for a clinically relevant *in vivo* inhibition of CYP2C9 by sorafenib may be expected to be low. However, patients taking warfarin or phenprocoumon should have their INR checked regularly (see section 4.4).

CYP3A4, CYP2D6 and CYP2C19 substrates

Concomitant administration of sorafenib and midazolam, dextromethorphan or omeprazole, which are substrates for cytochromes CYP3A4, CYP2D6 and CYP2C19 respectively, did not alter the exposure of these agents. This indicates that sorafenib is neither an inhibitor nor an inducer of these cytochrome P450 isoenzymes. Therefore, clinical pharmacokinetic interactions of sorafenib with substrates of these enzymes are unlikely.

UGT1A1 and UGT1A9 substrates

In vitro, sorafenib inhibited glucuronidation via UGT1A1 and UGT1A9. The clinical relevance of this finding is unknown (see below and section 4.4).

In vitro studies of CYP enzyme induction

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

P-gp-substrates

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

Combination with other anti-neoplastic agents

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

Paclitaxel/carboplatin

- Administration of paclitaxel (225 mg/m^2) and carboplatin (AUC = 6) with sorafenib (≤ 400 mg twice daily), administered with a 3-day break in sorafenib dosing (two days prior to and on the day of paclitaxel/carboplatin administration), resulted in no significant effect on the pharmacokinetics of paclitaxel.

- Co-administration of paclitaxel (225 mg/m^2, once every 3 weeks) and carboplatin (AUC=6) with sorafenib (400 mg twice daily, without a break in sorafenib dosing) resulted in a 47% increase in sorafenib exposure, a 29% increase in paclitaxel exposure and a 50% increase in 6-OH paclitaxel exposure. The pharmacokinetics of carboplatin were unaffected.

These data indicate no need for dose adjustments when paclitaxel and carboplatin are co-administered with sorafenib with a 3-day break in sorafenib dosing (two days prior to and on the day of paclitaxel/carboplatin administration). The clinical significance of the increases in sorafenib and paclitaxel exposure, upon co-administration of sorafenib without a break in dosing, is unknown.

Capecitabine

Co-administration of capecitabine (750-1050 mg/m^2 twice daily, Days 1-14 every 21 days) and sorafenib (200 or 400 mg twice daily, continuous uninterrupted administration) resulted in no significant change in sorafenib exposure, but a 15-50% increase in capecitabine exposure and a 0-52% increase in 5-FU exposure. The clinical significance of these small to modest increases in capecitabine and 5-FU exposure when co-administered with sorafenib is unknown.

Doxorubicin/Irinotecan

Concomitant treatment with sorafenib resulted in a 21 % increase in the AUC of doxorubicin. When administered with irinotecan, whose active metabolite SN-38 is further metabolised by the UGT1A1 pathway, there was a 67 - 120 % increase in the AUC of SN-38 and a 26 - 42 % increase in the AUC of irinotecan. The clinical significance of these findings is unknown (see section 4.4).

Docetaxel

Docetaxel (75 or 100 mg/m^2 administered once every 21 days) when co-administered with sorafenib (200 mg twice daily or 400 mg twice daily administered on Days 2 through 19 of a 21-day cycle with a 3-day break in dosing around administration of docetaxel) resulted in a 36-80 % increase in docetaxel AUC and a 16-32 % increase in docetaxel C_{max}. Caution is recommended when sorafenib is co-administered with docetaxel (see section 4.4).

Combination with other agents

Neomycin
Co-administration of neomycin, a non-systemic antimicrobial agent used to eradicate gastrointestinal flora, interferes with the enterohepatic recycling of sorafenib (see section 5.2, Metabolism and Elimination), resulting in decreased sorafenib exposure. In healthy volunteers treated with a 5-day regimen of neomycin the average exposure to sorafenib decreased by 54%. Effects of other antibiotics have not been studied, but will likely depend on their ability to interfere with microorganisms with glucuronidase activity.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no data on the use of sorafenib in pregnant women. Studies in animals have shown reproductive toxicity including malformations (see section 5.3). In rats, sorafenib and its metabolites were demonstrated to cross the placenta and sorafenib is anticipated to cause harmful effects on the foetus. Sorafenib should not be used during pregnancy unless clearly necessary, after careful consideration of the needs of the mother and the risk to the foetus.
Women of childbearing potential must use effective contraception during treatment.

Lactation

It is not known whether sorafenib is excreted in human milk. In animals, sorafenib and/or its metabolites were excreted in milk. Because sorafenib could harm infant growth and development (see section 5.3), women must not breast-feed during sorafenib treatment.

Fertility

Results from animal studies further indicate that sorafenib can impair male and female fertility (see section 5.3).

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

The most important serious adverse reactions were myocardial infarction/ischaemia, gastrointestinal perforation, drug induced hepatitis, haemorrhage, and hypertension/hypertensive crisis.

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

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

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

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

System organ class	Very common	Common	Uncommon	Rare	Not known
Infections and infestations	infection	folliculitis			
Blood and lymphatic system disorders	lymphopenia	leucopenia neutropenia anaemia thrombocytopenia			
Immune system disorders			hypersensitivity reactions (including skin reactions and urticaria) anaphylactic reaction	angioedema	
Endocrine disorders		hypothyroidism	hyperthyroidism		
Metabolism and nutrition disorders	anorexia hypo-phosphataemia	hypocalcaemia hypokalaemia hyponatraemia	dehydration		
Psychiatric disorders		depression			
Nervous system disorders		peripheral sensory neuropathy dysgeusia	reversible posterior leukoencephalo-pathy*		encephalopathy °
Ear and labyrinth disorders		tinnitus			
Cardiac disorders		congestive heart failure* myocardial ischaemia and infarction*		QT prolongation	
Vascular disorders	haemorrhage (inc. gastrointestinal *, respiratory tract* and cerebral haemorrhage*) hypertension	flushing	hypertensive crisis*		

System organ class	Very common	Common	Uncommon	Rare	Not known
Respiratory, thoracic and mediastinal disorders		rhinorrhoea dysphonia	interstitial lung disease-like events* (pneumonitis, radiation pneumonitis, acute respiratory distress, etc.)		
Gastro-intestinal disorders	diarrhoea nausea vomiting constipation	stomatitis (including dry mouth and glossodynia) dyspepsia dysphagia gastro oesophageal reflux disease	pancreatitis gastritis gastrointestinal perforations*		
Hepatobiliary disorders			increase in bilirubin and jaundice, cholecystitis, cholangitis	drug induced hepatitis*	
Skin and subcutaneous tissue disorders	dry skin rash alopecia hand foot skin reaction** erythema pruritus	keratoacanthoma/ squamous cell cancer of the skin dermatitis exfoliative acne skin desquamation hyperkeratosis	eczema erythema multiforme	radiation recall dermatitis Stevens-Johnson syndrome leucocytoclastic vasculitis toxic epidermal necrolysis*	
Musculo-skeletal and connective tissue disorders	arthralgia	myalgia muscle spasms		rhabdomyolysis	
Renal and urinary disorders		renal failure proteinuria		nephrotic syndrome	
Reproductive system and breast disorders		erectile dysfunction	gynaecomastia		

System organ class	Very common	Common	Uncommon	Rare	Not known
General disorders and administration site conditions	fatigue pain (including mouth, abdominal, bone, tumour pain and headache) fever	asthenia influenza like illness mucosal inflammation			
Investigations	weight decreased increased amylase increased lipase	transient increase in transaminases	transient increase in blood alkaline phosphatase INR abnormal, prothrombin level abnormal		

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

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

° Cases have been reported in the post marketing setting.

Further information on selected adverse drug reactions

Congestive heart failure

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

Additional information on special populations

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

Laboratory test abnormalities in HCC (study 3) and RCC (study 1) patients

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

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

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

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

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

Laboratory test abnormalities in DTC patients (study 5)

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

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

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

Laboratory parameter, (in % of samples investigated)	Sorafenib N=207			Placebo N=209		
	All Grades*	Grade 3*	Grade 4*	All Grades*	Grade 3*	Grade 4*
Blood and lymphatic system disorders						
Anemia	30.9	0.5	0	23.4	0.5	0
Thrombocytopenia	18.4	0	0	9.6	0	0
Neutropenia	19.8	0.5	0.5	12	0	0
Lymphopenia	42	9.7	0.5	25.8	5.3	0
Metabolism and nutrition disorders						
Hypokalemia	17.9	1.9	0	2.4	0	0
Hypophosphatemia**	19.3	12.6	0	2.4	1.4	0
Hepatobiliary disorders						
Bilirubin increased	8.7	0	0	4.8	0	0
ALT increased	58.9	3.4	1.0	24.4	0	0
AST increased	53.6	1.0	1.0	14.8	0	0
Investigations						
Amylase increased	12.6	2.4	1.4	6.2	0	1.0
Lipase increased	11.1	2.4	0	2.9	0.5	0

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

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

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic agents, protein kinase inhibitors, ATC code: L01XE05

Sorafenib is a multikinase inhibitor which has demonstrated both anti-proliferative and anti-angiogenic properties in vitro and in vivo.

Mechanism of action and pharmacodynamic effects

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

Clinical efficacy

The clinical safety and efficacy of sorafenib 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 study in 602 patients with hepatocellular carcinoma. Demographics and baseline disease characteristics were comparable between the sorafenib and the placebo group with regard to ECOG status (status 0: 54 % vs. 54 %; status 1: 38 % vs. 39 %; status 2: 8 % vs. 7 %), 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 %), and BCLC stage (stage B: 18.1 % vs. 16.8 %; stage C: 81.6 % vs. 83.2 %; stage D: < 1 % vs. 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 sorafenib over placebo for OS (HR: 0.69, p = 0.00058, see table 3).

There are limited data from this study in patients with Child Pugh B liver impairment and only one patient with Child Pugh C had been included.

Table 3: Efficacy results from study 3 (study 100554) in hepatocellular carcinoma

Efficacy Parameter	Sorafenib (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 (sorafenib over placebo)

* statistically significant as the p-value was below the prespecified O'Brien Fleming stopping boundary of 0.0077

** independent radiological review

A second Phase III, international, multi-centre, randomised, double blind, placebo-controlled study (Study 4, 11849) evaluated the clinical benefit of sorafenib in 226 patients with advanced hepatocellular carcinoma. This study, conducted in China, Korea and Taiwan confirmed the findings of Study 3 with respect to the favourable benefit-risk profile of sorafenib (HR (OS): 0.68, p = 0.01414).

In the pre-specified stratification factors (ECOG status, presence or absence of macroscopic vascular invasion and/or extrahepatic tumour spread) of both Study 3 and 4, the HR consistently favoured sorafenib over placebo. Exploratory subgroup analyses suggested that patients with distant metastases at baseline derived a less pronounced treatment effect.

Renal cell carcinoma

The safety and efficacy of sorafenib in the treatment of advanced renal cell carcinoma (RCC) were investigated in two clinical studies:

Study 1 (study 11213) was a Phase III, multi-centre, randomised, double blind, placebo-controlled study in 903 patients. Only patients with clear cell renal carcinoma and low and intermediate risk MSKCC (Memorial Sloan Kettering Cancer Center) were included. The primary endpoints were overall survival and progression-free survival (PFS).
Approximately half of the patients had an ECOG performance status of 0, and half of the patients were in the low risk MSKCC prognostic group.
PFS was evaluated by blinded independent radiological review using RECIST criteria. The PFS analysis was conducted at 342 events in 769 patients. The median PFS was 167 days for patients randomised to sorafenib compared to 84 days for placebo patients (HR = 0.44; 95 % CI: 0.35 - 0.55; p < 0.000001). Age, MSKCC prognostic group, ECOG PS and prior therapy did not affect the treatment effect size.

An interim analysis (second interim analysis) for overall survival was conducted at 367 deaths in 903 patients. The nominal alpha value for this analysis was 0.0094. The median survival was 19.3 months for patients randomised to sorafenib compared to 15.9 months for placebo patients (HR = 0.77; 95 % CI: 0.63 - 0.95; p = 0.015). At the time of this analysis, about 200 patients had crossed-over to sorafenib from the placebo group.

Study 2 was a Phase II, discontinuation study in patients with metastatic malignancies, including RCC. Patients with stable disease on therapy with sorafenib were randomised to placebo or continued sorafenib therapy. Progression-free survival in patients with RCC was significantly longer in the sorafenib group (163 days) than in the placebo group (41 days) (p = 0.0001, HR = 0.29).

Differentiated thyroid carcinoma (DTC)

Study 5 (study 14295) was a Phase III, international, multi-centre, randomised, double blind, placebo-controlled trial in 417 patients with locally advanced or metastatic DTC refractory to radioactive iodine. Progression-free survival (PFS) as evaluated by a blinded independent radiological review using RECIST criteria was the primary endpoint of the study. Secondary endpoints included overall survival (OS), tumour response rate and duration of response. Following progression, patients were allowed to receive open label sorafenib.
Patients were included in the study if they experienced progression within 14 months of enrollment and had DTC refractory to radioactive iodine (RAI). DTC refractory to RAI was defined as having a lesion without iodine uptake on a RAI scan, or receiving cumulative RAI $\geq$ 22.2 GBq, 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. The median delivered cumulative radioactive iodine activity before enrollment was approximately 14.8 GBq. Majority of patients had papillary carcinoma (56.8%), followed by follicular (25.4%) and poorly differentiated carcinoma (9.6%).

Median PFS time was 10.8 months in the sorafenib group compared to 5.8 months in the placebo group (HR=0.587; 95% Confidence Interval (CI): 0.454, 0.758; one-sided p <0.0001).
The effect of sorafenib on PFS was consistent independent of geographic region, age above or below 60 years, gender, histological subtype, and presence or absence of bone metastasis.

In an overall survival analysis conducted 9 months after the data cut-off for the final PFS analysis there was no statically significant difference in overall survival between the treatment groups (HR=0.884; 95% CI: 0.633, 1.236, one-sided p value of 0.236). The median OS was not reached in the sorafenib arm and was 36.5 months in the placebo arm. One hundred fifty seven (75%) patients randomised to placebo and 61 (30%) patients randomised to sorafenib received open-label sorafenib.

The median duration of therapy in the double-blind period was 46 weeks (range 0.3-135) for patients receiving sorafenib and 28 weeks (range 1.7–132) for patients receiving placebo.

No complete response (CR) according to RECIST was observed. The overall response rate (CR + partial response (PR) per independent radiological assessment was higher in the sorafenib group (24 patients, 12.2%) 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 sorafenib treated patients who experienced a PR.

A post-hoc subgroup analysis by maximum tumour size showed a treatment effect for PFS in favour of sorafenib over placebo for patients with maximum tumour size of 1.5 cm or larger (HR 0.54 (95% CI: 0.41 - 0.71)) whereas a numerically lower effect was reported in patients with a maximum tumour size of less than 1.5 cm (HR 0.87 (95% CI: 0.40 - 1.89).

A post-hoc subgroup analysis by thyroid carcinoma symptoms at baseline showed a treatment effect for PFS in favour of sorafenib over placebo for both symptomatic and asymptomatic patients. The HR of progression free survival was 0.39 (95% CI: 0.21 - 0.72) for patients with symptoms at baseline and 0.60 (95% CI: 0.45 - 0.81) for patients without symptoms at baseline.

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 section 4.4).

Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies, in all subsets of the paediatric population, in kidney and renal pelvis carcinoma (excluding nephroblastoma, nephroblastomatosis, clear cell sarcoma, mesoblastic nephroma, renal medullary carcinoma and rhabdoid tumour of the kidney) and liver and intrahepatic bile duct carcinoma (excluding hepatoblastoma) and differentiated thyroid carcinoma (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Absorption and distribution

After administration of sorafenib tablets the mean relative bioavailability is 38 - 49 % when compared to an oral solution. The absolute bioavailability is not known. Following oral administration sorafenib reaches peak plasma concentrations in approximately 3 hours. When given with a high-fat meal sorafenib absorption was reduced by 30 % compared to administration in the fasted state.
Mean C_{max} and AUC increased less than proportionally beyond doses of 400 mg administered twice daily. *In vitro* binding of sorafenib to human plasma proteins is 99.5 %.
Multiple dosing of sorafenib for 7 days resulted in a 2.5- to 7-fold accumulation compared to single dose administration. Steady state plasma sorafenib concentrations are achieved within 7 days, with a peak to trough ratio of mean concentrations of less than 2.

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

Biotransformation and elimination

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

Sorafenib accounts for approximately 70 - 85 % of the circulating analytes in plasma at steady state. Eight metabolites of sorafenib have been identified, of which five have been detected in plasma. The main circulating metabolite of sorafenib in plasma, the pyridine N-oxide, shows *in vitro* potency similar to that of sorafenib. This metabolite comprises approximately 9 - 16 % of circulating analytes at steady state.

Following oral administration of a 100 mg dose of a solution formulation of sorafenib, 96 % of the dose was recovered within 14 days, with 77 % of the dose excreted in faeces, and 19 % of the dose excreted in urine as glucuronidated metabolites. Unchanged sorafenib, accounting for 51 % of the dose, was found in faeces but not in urine, indicating that biliary excretion of unchanged active substance might contribute to the elimination of sorafenib.

Pharmacokinetics in special populations

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

Paediatric population

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

Race

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

Renal impairment

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

Hepatic impairment

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

5.3 Preclinical safety data

The preclinical safety profile of sorafenib was assessed in mice, rats, dogs and rabbits.
Repeat-dose toxicity studies revealed changes (degenerations and regenerations) in various organs at exposures below the anticipated clinical exposure (based on AUC comparisons).
After repeated dosing to young and growing dogs effects on bone and teeth were observed at exposures below the clinical exposure. Changes consisted in irregular thickening of the femoral growth plate, hypocellularity of the bone marrow next to the altered growth plate and alterations of the dentin composition. Similar effects were not induced in adult dogs.

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

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

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

Environmental Risk assessment studies have shown that sorafenib tosylate has the potential to be persistent, bioaccumulative and toxic to the environment. Environmental Risk Assessment information is available in the EPAR of this medicine (see section 6.6).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:
Croscarmellose sodium
Microcrystalline cellulose
Hypromellose
Sodium laurilsulfate
Magnesium stearate

Tablet coating:
Hypromellose
Macrogol (3350)
Titanium dioxide (E 171)
Ferric oxide red (E 172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Do not store above 25°C.

6.5 Nature and contents of container

112 film-coated tablets (4 x 28) in transparent (PP/Aluminium) blister packs.

6.6 Special precautions for disposal

This medicinal product could have potential risk for the environment. Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Bayer Pharma AG
13342 Berlin
Germany

8. MARKETING AUTHORISATION NUMBER

EU/1/06/342/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 19 July 2006
Date of latest renewal: 21 July 2011

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

ANNEX II

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITION OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

Bayer Pharma AG
51368 Leverkusen
Germany

Bayer HealthCare Manufacturing Srl.
Via delle Groane, 126
20024 Garbagnate Milanese
Italy

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic Safety Update Reports**

The marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list)) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Nexavar 200 mg film-coated tablets
Sorafenib

2. STATEMENT OF ACTIVE SUBSTANCE

Each tablet contains 200 mg of sorafenib (as tosylate).

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

112 film-coated tablets

5. METHOD AND ROUTE OF ADMINISTRATION

Oral use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 25 °C.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Bayer Pharma AG
13342 Berlin
Germany

12. MARKETING AUTHORISATION NUMBER

EU/1/06/342/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Nexavar 200 mg

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER

1. NAME OF THE MEDICINAL PRODUCT

Nexavar 200 mg tablets
Sorafenib

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Bayer (Logo)

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

MON
TUE
WED
THU
FRI
SAT
SUN

B. PACKAGE LEAFLET

Package Leaflet: Information for the user
Nexavar 200 mg film-coated tablets
sorafenib

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Nexavar is and what it is used for

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

Nexavar is a so-called *multikinase inhibitor*. It works by slowing down the rate of growth of cancer cells and cutting off the blood supply that keeps cancer cells growing.

2. What do you need to know before you take Nexavar

Do not take Nexavar
- **If you are allergic** to sorafenib or any of the other ingredients of this medicine (listed in section 6).

Warnings and precautions
Talk to your doctor or pharmacist before taking Nexavar.

Take special care with Nexavar
- **If you experience skin problems.** Nexavar can cause rashes and skin reactions, especially on the hands and feet. These can usually be treated by your doctor. If not, your doctor may interrupt treatment or stop it altogether.
- **If you have high blood pressure.** Nexavar can raise blood pressure, and your doctor will usually monitor your blood pressure and may give you a medicine to treat your high blood pressure.
- **If you get any bleeding problems, or are taking warfarin or phenprocoumon.** Treatment with Nexavar may lead to a higher risk of bleeding. If you are taking warfarin or phenprocoumon, medicines which thin the blood to prevent blood clots, there may be a greater risk of bleeding.
- **If you get chest pain or heart problems**. Your doctor may decide to interrupt treatment or stop it altogether.
- **If you have a heart disorder**, such as an abnormal electrical signal called "prolongation of the QT interval".

- **If you are going to have surgery, or if you had an operation recently**. Nexavar might affect the way your wounds heal. You will usually be taken off Nexavar if you are having an operation. Your doctor will decide when to start with Nexavar again.
- **If you are taking irinotecan or are given docetaxel,** which are also medicines for cancer. Nexavar may increase the effects and, in particular, the side effects of these medicines.
- **If you are taking Neomycin or other antibiotics.** The effect of Nexavar may be decreased.
- **If you have severe liver impairment.** You may experience more severe side effects when taking this medicine.
- **If you have poor kidney function**. Your doctor will monitor your fluid and electrolyte balance.
- **Fertility.** Nexavar may reduce fertility in both men and women. If you are concerned, talk to a doctor.
- **Holes in the gut wall** (*gastrointestinal perforation*) may occur during treatment (see section 4: Possible Side Effects). In this case your doctor will interrupt the treatment.
- **If you have thyroid cancer.** Your doctor will monitor blood calcium and thyroid hormone levels.

Tell your doctor if any of these affect you. You may need treatment for them, or your doctor may decide to change your dose of Nexavar, or stop treatment altogether (see also section 4: Possible side effects).

Children and adolescents
Children and adolescents have not yet been tested with Nexavar.

Other medicines and Nexavar
Some medicines may affect Nexavar, or be affected by it. Tell your doctor or pharmacist if you are taking, have recently taken or might take anything in this list or any other medicines, including medicines obtained without a prescription:
- Rifampicin, Neomycin or other medicines used to treat infections (**antibiotics**)
- St John's wort, a herbal treatment for **depression**
- Phenytoin, carbamazepine or phenobarbital, treatments for **epilepsy** and other conditions
- Dexamethasone, a **corticosteroid** used for various conditions
- Warfarin or phenprocoumon, anticoagulants used to **prevent blood clots**
- Doxorubicin, capecitabine, docetaxel, paclitaxel and irinotecan, which are **cancer treatments**
- Digoxin, a treatment for mild to moderate **heart failure**

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

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

Driving and using machines
There is no evidence that Nexavar will affect the ability to drive or to operate machines.

3. How to take Nexavar

The recommended dose of Nexavar in adults is 2 x 200 mg tablets, twice daily.
This is equivalent to a daily dose of 800 mg or four tablets a day.

Swallow Nexavar tablets with a glass of water, either without food or with a low-fat or moderate fat meal. Do not take this medicine with high fat meals, as this may make Nexavar less effective. If you intend to have a high fat meal, take the tablets at least 1 hour before or 2 hours after the meal.
Always take this medicine exactly as your doctor has told you to. Check with your doctor or pharmacist if you are not sure.

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

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

If you take more Nexavar than you should
Tell your doctor straight away if you (or anyone else) have taken more than your prescribed dose. Taking too much Nexavar makes side effects more likely or more severe, especially diarrhoea and skin reactions. Your doctor may tell you to stop taking this medicine.

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

4. Possible side effects

Like all medicines, this medicine can cause side effects although not everybody gets them. This medicine may also affect the results of some blood tests.

Very common:
may affect more than 1 in 10 people
- diarrhoea
- feeling sick (*nausea*)
- feeling weak or tired *(fatigue)*
- pain (including mouth pain, abdominal pain, headache, bone pain, tumour pain)
- hair loss *(alopecia)*
- flushed or painful palms or soles *(hand foot skin reaction)*
- itching or rash
- throwing up *(vomiting)*
- bleeding (including bleeding in the brain, gut wall and respiratory tract; *haemorrhage*)
- high blood pressure, or increases in blood pressure *(hypertension)*
- infections
- loss of appetite *(anorexia)*
- constipation
- joint pain *(arthralgia)*
- fever
- weight loss
- dry skin

Common:
may affect up to 1 in 10 people
- flu-like illness
- indigestion *(dyspepsia)*
- difficulty swallowing *(dysphagia)*
- inflamed or dry mouth, tongue pain *(stomatitis and mucosal inflammation)*
- low calcium levels in the blood *(hypocalcaemia)*
- low potassium levels in the blood (*hypokalaemia*)
- muscle pain (*myalgia*)
- disturbed sensations in fingers and toes, including tingling or numbness *(peripheral sensory neuropathy)*
- depression
- erection problems (*impotence*)
- altered voice *(dysphonia)*
- acne

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

Uncommon:
may affect up to 1 in 100 people
- inflamed stomach lining (*gastritis*)
- pain in the tummy (*abdomen*) caused by pancreatitis, inflammation of the gall bladder and/or bile ducts
- yellow skin or eyes (*jaundice*) caused by high levels of bile pigments (*hyperbilirubinaemia*)
- allergic like reactions (including skin reactions and hives)
- dehydration
- enlarged breasts *(gynaecomastia)*
- breathing difficulty (*lung disease)*
- eczema
- overactive thyroid gland *(hyperthyroidism)*
- multiple skin eruptions (*erythema multiforme*)
- abnormally high blood pressure
- holes in the gut wall (*gastrointestinal perforation*)
- reversible swelling in the rear part of the brain that can be associated with headache, altered consciousness, fits and visual symptoms including visual loss (*reversible posterior leukoencephalopathy*)
- a sudden, severe allergic reaction *(anaphylactic reaction)*

Rare: may affect up to 1 in 1,000 people
- allergic reaction with swelling of the skin (e. g. face, tongue) that may cause difficulty in breathing or swallowing *(angioedema)*
- abnormal heart rhythm *(QT prolongation)*
- inflammation of the liver, which may lead to nausea, vomiting, abdominal pain, and jaundice (*drug induced hepatitis)*
- a sunburn-like rash that may occur on skin that has previously been exposed to radiotherapy and can be severe *(radiation recall dermatitis)*
- serious reactions of the skin and/or mucous membranes which may include painful blisters and fever, including extensive detachment of the skin *(Stevens-Johnson syndrome and toxic epidermal necrolysis)*
- abnormal muscle breakdown which can lead to kidney problems *(rhabdomyolysis)*
- damage of the kidney causing them to leak large amounts of protein *(nephrotic syndrome)*
- inflammation of the vessels in the skin which may result in rash *(leucocytoclastic vasculitis)*

Not known: frequency cannot be estimated from the available data
- impaired brain function that can be associated with e.g. drowsiness, behavioural changes, or confusion *(encephalopathy)*

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects, you can help provide more information on the safety of this medicine.

5. How to store Nexavar

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and on each blister after EXP. The expiry date refers to the last day of that month.

Do not store this medicine above 25°C.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Nexavar contains

- The **active** substance is sorafenib. Each film-coated tablet contains 200 mg sorafenib (as tosylate).
- The **other** ingredients are:
  Tablet core: croscarmellose sodium, microcrystalline cellulose, hypromellose, sodium laurilsulfate, magnesium stearate.
  Tablet coating: hypromellose, macrogol, titanium dioxide (E 171), ferric oxide red (E 172).

What Nexavar looks like and contents of the pack

Nexavar 200 mg film-coated tablets are red and round with the Bayer cross on one side and "200" on the other side. They come in calendar packs of 112 tablets: four transparent blister packs of 28 tablets each.

Marketing Authorisation Holder
Bayer Pharma AG
13342 Berlin
Germany

Manufacturer
Bayer Pharma AG
51368 Leverkusen
Germany

Bayer HealthCare Manufacturing Srl.
Via delle Groane, 126
20024 Garbagnate Milanese
Italy

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder .

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Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu.