NEXAVAR®

Film Coated Tablet

Important information, please read carefully!

COMPOSITION

Each Nexavar® film-coated tablet contains 274 mg sorafenib tosylate correspond to 200 mg of sorafenib.

PHARMACEUTICAL FORM

Red round, faceted biconvex film coated tablet, with the Bayer cross on one side and “200” on the other side and with a diameter of 10 mm and a weight of 350 mg.

INDICATIONS

- NEXAVAR® is indicated for the treatment of patients with advanced renal cell carcinoma.
- NEXAVAR® is indicated for the treatment of patients with unresectable hepatocellular carcinoma (HCC).

POSOLOGY AND METHOD OF ADMINISTRATION

Recommended dose
The recommended daily dose of sorafenib is 400 mg (2 x 200 mg tablets) taken twice a day, without food (at least 1 hour before or 2 hours after eating).

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 Unresectable 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 unresectable hepatocellular carcinoma (HCC) and advanced renal cell carcinoma (RCC), the sorafenib dose should be reduced to two tablets of 200 mg once daily (see ***section Special Warnings and Precautions For Use***).

Suggested dose modifications for skin toxicity are outlined in Table 1.

Table 1: Suggested Dose Modifications for Skin Toxicity with Unresectable HCC and RCC

Skin Toxicity Grade	Occurrence	Suggested Dose Modification
Grade 1: Numbness, dysesthesia, paresthesia, tingling, painless swelling, erythema or discomfort of the hands or feet which does not disrupt the patient’s normal activities	Any occurrence	Continue treatment with NEXAVAR and consider topical therapy for symptomatic relief.
Grade 2: Painful erythema and swelling of the hands or feet and/or discomfort affecting the patient’s normal activities	1st occurrence	Continue treatment with NEXAVAR and consider topical therapy for symptomatic relief If no improvement within 7 days, see below.

	No improvement within 7 days or 2nd or 3rd occurrence	Interrupt NEXAVAR treatment until toxicity resolves to Grade 0-1 When resuming treatment, decrease NEXAVAR dose by one dose level (400 mg daily or 400 mg every other day)
	4th occurrence	Discontinue NEXAVAR treatment
Grade 3: Moist desquamation, ulceration, blistering or severe pain of the hands or feet, or severe discomfort that causes the patient to be unable to work or perform activities of daily living	1st or 2nd occurrence	Interrupt NEXAVAR treatment until toxicity resolves to Grade 0-1 When resuming treatment, decrease NEXAVAR dose by one dose level (400 mg daily or 400 mg every other day)
	3rd occurrence	Discontinue NEXAVAR treatment

Special populations
Pediatric Patients
The safety and effectiveness of sorafenib in children and adolescents (< 18 years) have not been established. Nexavar is not recommended for use in children and adolescents due to a lack of data on safety and efficacy.

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 ***section Pharmacokinetic Properties - Special Populations - Hepatic Impairment***).

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

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

PROPERTIES

PHARMACODYNAMIC PROPERTIES
Pharmacotherapeutic group: Antineoplastic agents, protein kinase inhibitors, ATC code: L01EX02.

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 tumor cell proliferation in vitro.
Sorafenib inhibits tumor growth of human tumor xenografts in athymic mice accompanied by a reduction of tumor angiogenesis.

Sorafenib inhibits the activity of targets present in the tumor cell (CRAF, BRAF, V600E BRAF, c-KIT, and FLT-3) and in the tumor 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 Nexavar have been studied in patients with hepatocellular carcinoma (HCC) and in patients with advanced renal cell carcinoma (RCC).

Hepatocellular Carcinoma

Study 3 (study 100554) was a Phase III, international, multi centre, randomized, double blind, placebo controlled study in 602 patients with hepatocellular carcinoma. Demographics and baseline disease characteristics were comparable between the Nexavar 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 Nexavar over placebo for OS (HR: 0.69, P = 0.00058, See Table 2). In the prespecified stratification factors (ECOG status, presence or absence of macroscopic vascular invasion and/or extrahepatic tumor spread) the hazard ratio consistently favoured Nexavar over placebo. The descriptive subgroup analysis suggested a potentially less pronounced treatment effect for the subgroups of patients below 65 years of age and those with metastatic disease. 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 2 : 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

Renal Cell Carcinoma

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

Study 1 was a Phase III, international, multi-centre, randomized, double blind, placebo-controlled study in 903 patients. Primary study endpoints included overall survival and progression-free survival (PFS). Tumor response rate was a secondary endpoint.

Patients were randomized 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 Center) prognostic group.

In a planned interim analysis of survival based on 220 deaths, there was an estimated 39% improvement in overall survival for patients receiving Nexavar vs. placebo. The estimated hazard ratio (risk of death with Nexavar 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).

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 randomized to Nexavar (167 days) compared to placebo patients (84 days) (HR =0.44; 95% CI: 0.35-0.55; p<0.000001).

The effect on PFS was also explored across different patient subsets. The subsets included age above or below 65 years, ECOG PS 0 or 1, MSKCC prognostic risk category 1, whether the prior therapy was for progressive metastatic disease or for an earlier disease setting, and time from diagnosis of less than or greater than 1.5 years. The effect of Nexavar on PFS was consistent across these subsets, including patients with no prior IL-2 or interferon therapy (n=137; 65 patients receiving Nexavar and 72 placebo), for whom the median PFS was 172 days on Nexavar compared to 85 days on placebo.

Best overall tumor response was determined by investigator radiological review according to RECIST criteria. In the Nexavar 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 partial response, and 239 patients (52.9%) had stable disease.

Nexavar 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 Nexavar 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 2 was a Phase II randomized discontinuation trial in patients with metastatic malignancies, including RCC. The primary endpoint of the study was the percentage of randomized patients (N= 65) remaining progression-free at 24 weeks. Progression-free survival was significantly longer in the Nexavar 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 randomized to Nexavar (50%) than in the placebo patients (18%) (p=0.0077).

PHARMACOKINETIC PROPERTIES

Absorption and Distribution

After administration of sorafenib tablets, the mean relative bioavailability is 38-49% when compared to an oral solution.

Following oral administration, sorafenib reaches peak plasma levels in approximately 3 hours. When given with a moderate-fat meal, bioavailability is similar to that in the fasted state. With a high-fat meal, sorafenib bioavailability is reduced by 29% compared to administration in the fasted state. It is recommended that sorafenib be administered without food (at least 1 hour before or 2 hours after eating).

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

Metabolism

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

Following oral administration of a 100 mg dose of a solution formulation of sorafenib, 96% of the dose was recovered within 14 days, with 77% of the dose excreted in feces, and 19% of the dose excreted in urine as glucuronidated metabolites. Unchanged sorafenib, accounting for 51% of the dose, was found in feces but not in urine.
The elimination half-life of sorafenib is approximately 25-48 hours.

Linearity/Non-linearity

Mean C_{max} and AUC increase less than proportionally beyond doses of 400 mg administered orally twice daily.

Steady-state Pharmacokinetics

Multiple dosing of sorafenib for 7 days results in a 2.5 to 7 fold accumulation compared to single dose administration.
Steady state plasma sorafenib concentrations are achieved within 7 days, with a peak to trough ratio of mean concentrations of less than 2.

Studies on enzyme inhibition

Studies with human liver microsomes demonstrated that sorafenib is a competitive inhibitor of CYP2C19, CYP2D6, and CYP3A4. Sorafenib may increase the blood level of drugs that are substrates of these enzymes.
In vitro data show that Sorafenib inhibits glucuronidation by the UGT1A1 and UGT1A9 pathways. Systemic exposure to substrates of UGT1A1 and UGT1A9 may be increased when co-administered with sorafenib.
Sorafenib inhibits CYP2B6 and CYP2C8 in vitro with K_i values of 6 and 1–2 µM, respectively. Systemic exposure to substrates of CYP2B6 and CYP2C8 may increase when co-administered with sorafenib.

Concomitant administration of sorafenib with cyclophosphamide resulted in a small decrease in cyclophosphamide exposure, but no decrease in the systemic exposure of 4-OH cyclophosphamide, the active metabolite of cyclophosphamide that is formed primarily by CYP2B6. These data suggest that sorafenib may not be an in vivo inhibitor of CYP2B6.

Studies with human liver microsomes demonstrated that sorafenib is a competitive inhibitor of CYP2C9 with a K_i 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.

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.

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, irinotecan, and 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 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 35% 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 small 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, Days 1-14 every 21 days) and sorafenib (200 or 400 mg twice daily, continuous uninterrupted administration) resulted in no significant change in sorafenib exposure, but a 15-50% increase in capecitabine exposure and a 0-52% increase in 5-FU exposure. The clinical significance of these small to modest increases in capecitabine and 5-FU exposure upon co-administered with sorafenib is unknown.

Doxorubicin/Irinotecan

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

Docetaxel

Docetaxel (75 or 100 mg/m^2 administered once every 21 days) when co-administered with sorafenib (200 mg twice daily or 400 mg twice daily administered on Day 2 through 19 of a 21-day cycle), with a 3-day break in dosing, around administration of docetaxel, resulted in a 36-80% increase in docetaxel AUC and a 16-32% increase in docetaxel Cmax. Caution is recommended when sorafenib is co-administered with docetaxel (*see* ***section Special Warnings and Precautions For Use***).

Combination with antibiotics

Neomycin

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

Combination with proton pump inhibitors

Omeprazole
Co-administration 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 ***section Special Warnings and Precautions For Use***).

Sorafenib is mainly eliminated via the liver, and exposure might be increased in this patient population

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 of 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.

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.

Based on the proposed mechanism of multikinase inhibition and multiple adverse effects seen in animals at exposure levels significantly below the clinical dose, sorafenib should be assumed to cause fetal harm when administered to a pregnant woman.

Breastfeeding should be discontinued during sorafenib therapy.
(see ***section Pregnancy and Lactation***).

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

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

Hemorrhage: An increase in the risk of bleeding may occur following sorafenib administration. The incidence of severe bleeding events is uncommon. If any bleeding event necessitates medical intervention, it is recommended that permanent discontinuation of sorafenib should be considered (see ***section Undesirable Effects***).

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

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 NEXAVAR group (2.9%) compared with the placebo group (0.4%). In Study 100554, the incidence of treatment-emergent cardiac ischemia/infarction events was 2.7% in sorafenib patients compared with 1.3% in the placebo group. Patients with unstable coronary artery disease or recent myocardial infarction were excluded from these studies. Temporary or permanent discontinuation of NEXAVAR should be considered in patients who develop cardiac ischemia and/or infarction (see ***section Undesirable Effects, Pharmacokinetic Properties - Clinical Efficacy***).

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

Hepatic impairment: No data is available on patients with Child Pugh C (severe) hepatic impairment. Since sorafenib is mainly eliminated via the hepatic route, exposure might be increased in patients with severe hepatic impairment (see ***section Pharmacokinetic Properties***).

Drug-Drug Interactions:
UGT1A1 pathway : Caution is recommended when administering sorafenib together with compounds that are metabolized/eliminated predominantly by the UGT1A1 pathway (e.g. irinotecan). (see ***section interactions***)

Docetaxel : Concomitant use of docetaxel (75 or 100 mg/m^2 administered every 21 days) with sorafenib (200 mg 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 and a 16 – 32 % increase in docetaxel Cmax. Caution is recommended when sorafenib is co-administered with docetaxel (see ***section interactions***)

Doxorubicin : concomitant treatment with Nexavar resulted in a 21% increase in the AUC of doxorubicin. Caution is recommended when administering doxorubicin with Nexavar. (see ***section Interactions***).

Neomycin : Co-administration of neomycin may cause a decrease in sorafenib bioavailability (see Interactions)

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

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), rash.

Table 3a: Adverse Events Reported in at Least 5% of Patients in Any Treatment Group – Study 11213 in Renal Cell carcinoma.

		Nexavar N=451			Placebo N=451		
System Organ Class	**Preferred Term**	**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	diarrhea	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%
	pruritis	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	pain in extremity	6%	<1%	0%	2%	0%	0%
	arthralgia	6%	<1%	0%	3%	0%	0%
General Disorders and Administrative Site conditions	fatigue	15%	2%	0%	12%	<1%	0%
	asthenia	9%	<1%	0%	4%	<1%	0%

Table 3b: Adverse reactions reported in at least 5% of patients in any treatment group – Study 100554 in hepatocellular carcinoma

		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 %

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

Adverse reactions that occurred either during clinical studies or have been identified through postmarketing use are listed below in Table 4, 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 4: All adverse drug reactions reported in patients in multiple clinical trials or through post-marketing use

System Organ Class	Very Common ≥ 1/10	Common ≥ 1/100 to < 1/10	Uncommon ≥ 1/1,000 to < 1/100	Rare ≥ 1/10,000 to < 1/1,000)	Not Known
Infections and Infestations	infection	folliculitis			
Blood and Lymphatic System Disorders	lymphopenia	leucopenia neutropenia anaemia thrombocytopenia			
Immune System Disorders			anaphylactic reaction hypersensitivity reactions (including skin reactions and urticaria)		angioedema
Endocrine Disorders		hypothyroidism	hyperthyroidism		
Metabolism and Nutrition Disorders	anorexia hypophosphataemia	hypocalcaemia hypokalemia hyponatraemia	dehydration		
Psychiatric Disorders		depression			
Nervous System Disorders		peripheral sensory neuropathy dysguesia	reversible posterior leukoencephalopathy*		

System Organ Class	Very Common ≥ 1/10	Common ≥ 1/100 to < 1/10	Uncommon ≥ 1/1,000 to < 1/100	Rare ≥ 1/10,000 to < 1/1,000)	Not Known
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* (includes reports of pneumonitis, radiation pneumonitis, acute respiratory distress, interstitial pneumonia, pulmonitis and lung inflammation)		
Gastrointestinal Disorders	diarrhoea nausea vomiting constipation	stomatitis (including dry mouth and glossodynia) dyspepsia dysphagia mucositis 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** pruritus erythema	keratoacanthoms/ squamous cell cancer of the skin dermatitis exfoliative acne skin desquamation hyperkeratosis	eczema erythema multiforme		radiation recall dermatitis Steven-Johnson Syndrome leukocytoclastic vasculitis toxic epidermal necrolysis*

System Organ Class	Very Common ≥ 1/10	Common ≥ 1/100 to < 1/10	Uncommon ≥ 1/1,000 to < 1/100	Rare ≥ 1/10,000 to < 1/1,000)	Not Known
Musculoskeletal, Connective Tissue and Bone Disorders	arthralgia	myalgia muscle spasms			rhabdomyolysis
Renal and Urinary Disorders		renal failure proteinuria		nephrotic syndrome	
Reproductive System and Breast Disorders		erectile dysfunction	gynaecomastia		
General Disorders and Administration Site Conditions	fatigue pain (including mouth, abdominal, bone, tumour pain and headache) fever	asthenia influenza like illness mucosal inflammation			
Investigations	weight decreased increased amylase increased lipase	transient increase in transaminases	transient increase in blood alkaline phosphatase, INR abnormal, prothrombin level abnormal		

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

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 aetiology of hypophosphataemia associated with sorafenib is not known.
CTCAE grade 3 or 4 were reported for lymphopenia in 13% of sorafenib treated patients and 7% of placebo patients, for neutropenia in 5% of sorafenib treated patients and 2% of placebo patients, for anaemia in 2% of sorafenib treated patients and 4% of placebo patients and for thrombocytopenia in 1% of sorafenib treated patients and 0% of placebo patients.

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).

Hypophosphataemia was a common laboratory finding, observed in 35% of NEXAVAR-treated patients compared to 11% of placebo patients; CTCAE grade 3 hypophosphataemia (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 hypophosphataemia (< 1 mg/dl) reported in the placebo group. The etiology of hypophosphataemia associated with NEXAVAR is not known.

Elevations in liver function tests were comparable between the 2 arms of the study. 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.
INR elevations were observed in 42% of NEXAVAR-treated patients; CTCAE Grade 3 INR elevations were reported in 4% of NEXAVAR-treated patients and 2% of placebo patients; there was no CTCAE Grade 4 INR elevation in either group.
Lymphopenia was observed in 47% of NEXAVAR-treated patients and 42% of placebo patients.
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.

Reporting of suspected adverse drug reaction

Reporting suspected adverse reaction after product authorization is crucial for ongoing benefit-risk monitoring. Healthcare professionals are requested to report any suspected adverse reactions to PT Bayer Indonesia through email at drugsafety.indonesia@bayer.com.

CONTRA-INDICATIONS

Sorafenib is contraindicated in patients with known severe hypersensitivity to sorafenib or any of the excipients.

INTERACTION WITH OTHER MEDICAMENTS 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 increase metabolism of sorafenib and thus decrease sorafenib concentrations.

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

CYP2C9 substrates: The possible effect of sorafenib on warfarin, a CYP2C9 substrate, was assessed in sorafenib-treated patients compared to placebo treated patients. The concomitant treatment with sorafenib and warfarin did not result in changes in mean PT-INR compared to placebo. However, patients taking warfarin should have their INR checked regularly (see ***section Warnings and Precautions For Use***).

CYP isoform-selective substrates: Concomitant administration of midazolam, dextromethorphan and omeprazole, which are substrates of cytochromes CYP3A4, CYP2D6 and CYP2C19, respectively, following 4 weeks of sorafenib administration did not alter the exposure of these agents. This indicates

that sorafenib is neither an inhibitor nor an inducer of these cytochrome P450 isoenzymes. In a separate clinical study, concomitant administration of sorafenib with paclitaxel resulted in an increase, instead of a decrease, in the exposure of 6-OH paclitaxel, the active metabolite of paclitaxel that is formed by CYP2C8. These data suggest that sorafenib may not be an *in vivo* inhibitor of CYP2C8. In another clinical study, concomitant administration of sorafenib with cyclophosphamide resulted in a small decrease in cyclophosphamide exposure, but no decrease in the systemic exposure of 4-OH cyclophosphamide, the active metabolite of cyclophosphamide that is formed primarily by CYP2B6. These data suggest that sorafenib may not be an in vivo inhibitor of CYP2B6.

Combination with other anti-neoplastic agents: In clinical studies, sorafenib has been administered together with a variety of other anti-neoplastic agents at their commonly used dosing regimens, including gemcitabine, cisplatin, oxaliplatin, paclitaxel, carboplatin, capecitabine, doxorubicin, irinotecan, and 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 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 ***section Special Warnings and Precautions For Use***).

Docotaxel: Docetaxel (75 or 100 mg/m^2 administered once every 21 days) when co-administered with sorafenib (200 mg twice daily or 400 mg twice daily administered on Day 2 through 19 of a 21-day cycle), with a 3-day break in dosing, around administration of docetaxel, resulted in a 36-80% increase in docetaxel AUC and a 16-32% increase in docetaxel Cmax. Caution is recommended when sorafenib is co-administered with docetaxel (see ***section Special Warning 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 Clinical Pharmacology, Metabolism and Elimination), resulting in decreased sorafenib exposure. In healthy volunteers treated with a 5-day regimen of neomycin the average bioavailability of sorafenib decreased by 54%. The clinical significance of these findings is unknown. Effects of other antibiotics have not been studied, but will likely depend on their ability to decrease glucuronidase activity.

Combination with proton pump inhibitors

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

FERTILITY, 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* ***section 5.3***). In rats, sorafenib and its metabolites were demonstrated to cross the placenta and sorafenib is anticipated to inhibit angiogenesis in the fetus.

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 (see ***section Special Warnings and Precautions For Use***).

Women of childbearing-potential/Contraception

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.

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, woman should discontinue breastfeeding during sorafenib treatment.

Fertility

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

EFFECTS ON ABILITY TO DRIVE AND 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.

OVERDOSE

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

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 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 at a daily sorafenib dose of 600 mg/m2 body surface area (equivalent to 1.2 times the recommended clinical dose of 500 mg/m2 on a body surface area basis), hypocellularity of the bone marrow next to the altered growth plate at 200 mg/m2/day, and alterations of the dentin composition at 600 mg/m2/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.

In a 2-year mouse carcinogenicity study there were cases of colon adenocarcinoma associated with severe hyperplasia and inflammation, and in a 2-year rat carcinogenicity study there were cases of pancreatic islet cell adenoma. Systemic exposures achieved in both carcinogenicity studies were below clinical exposures in humans at the recommended dose. The observed cases were few in numbers and the clinical relevance of these findings is unknown.

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 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 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/m2/day in rats and 36 mg/m2/day in rabbits (see ***Special Warnings and Precautions For Use and Pregnancy and Lactation***).

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.

PRESENTATION

Box, 6 blisters @ 10 film-coated tablets.

STORAGE

Store below 30^{o}C

Reg. No. DKIXXXXXXXXXXX

Harus dengan resep dokter

Manufactured by Patheon France S.A.S., Bourgoin-Jallieu – France
Packed and released by Bayer AG, Leverkusen – Germany

Imported by PT Bayer Indonesia, Depok - Indonesia

Brosur kemasan: Informasi untuk Pasien

Nexavar® tablet salut selaput 200 mg
Sorafenib

Bacalah seluruh isi brosur ini dengan saksama sebelum Anda mulai mengonsumsi obat karena terdapat informasi yang penting bagi Anda.
- Simpan brosur ini. Anda mungkin memerlukannya nanti.
- Jika ada pertanyaan lebih lanjut, tanyakan kepada Dokter atau Apoteker Anda.
- Obat ini diresepkan khusus untuk Anda. Jangan berikan kepada orang lain. Hal ini dapat membahayakan mereka meskipun mereka memiliki gejala penyakit yang sama dengan Anda.
- Jika Anda mengalami efek samping apapun, konsultasikan dengan Dokter atau Apoteker. Termasuk juga kemungkinan efek samping yang tidak tercantum dalam brosur ini.

Isi brosur ini

1. Apa itu Nexavar dan apa kegunaannya

Nexavar digunakan untuk mengobati kanker hati (*hepatocellular carcinoma*).
Nexavar digunakan untuk mengobati kanker ginjal *(renal cell carcinoma*).
Nexavar merupakan *penghambat multikinase.* Cara kerjanya ialah dengan memperlambat pertumbuhan sel kanker dan menghentikan pasokan darah yang mendukung pertumbuhan sel kanker.

2. Hal yang perlu Anda ketahui sebelum mengonsumsi

Jangan mengonsumsi Nexavar
- Jika Anda alergi (hipersensitif) terhadap sorafenib, komponen aktif Nexavar, atau komponen Nexavar lainnya. Komponen Nexavar tertera di halaman akhir brosur ini.

Berhati-hatilah saat mengonsumsi Nexavar
- Jika sedang mengupayakan kehamilan atau merasa sedang hamil, beri tahu dokter Anda. Nexavar dilarang dikonsumsi selama kehamilan. (lihat informasi di bawah)
- Menyusui harus dihentikan selama terapi pengobatan dengan sorafenib. (lihat informasi di bawah)
- Jika Anda mengalami masalah kulit. Nexavar dapat menyebabkan ruam dan reaksi pada kulit, khususnya di tangan dan kaki. Kulit biasanya tampak berbeda selama enam minggu pertama pengobatan dengan sorafenib. Jika melihat perbedaan ini, hubungi dokter agar pengobatan bisa dilakukan. Dokter Anda mungkin menyarankan pengobatan kulit dan/atau perubahan dosis Nexavar. Jika kulit tak kunjung kembali ke kondisi semula, dokter Anda mungkin menghentikan pengobatan dengan Nexavar.
- Jika Anda menderita tekanan darah tinggi. Nexavar dapat menaikkan tekanan darah dan dokter Anda akan memantau tekanan darah Anda dan mungkin memberi obat untuk mengatasi tekanan darah tinggi.
- Jika Anda mengalami perdarahan atau mengonsumsi warfarin. Pengobatan dengan Nexavar mungkin meningkatkan risiko perdarahan. Jika mengonsumsi warfarin atau obat pengencer darah untuk mencegah gumpalan darah, Anda mungkin lebih berisiko mengalami perdarahan.
- Jika Anda akan menjalani pembedahan atau baru menjalani pembedahan. Nexavar mungkin memengaruhi proses penyembuhan luka bedah. Pengobatan dengan Nexavar biasanya dihentikan jika Anda akan menjalani pembedahan. Dokter akan menetapkan kapan Anda perlu melanjutkan konsumsi Nexavar.
- Jika Anda mengalami nyeri dada atau masalah jantung. Dokter mungkin menunda atau menghentikan pengobatan Anda.
- Jika Anda mengalami kelainan ritme jantung yang disebut perpanjangan interval QT. Nexavar mungkin mengganggu ritme jantung.
- Perforasi usus (*perforasi gastrointestinal*) mungkin terjadi selama pengobatan (lihat *Kemungkinan Efek Samping*, bagian 4). Dalam hal ini, dokter mungkin menghentikan pengobatan.
- Jika Anda mengalami masalah hati serius. Anda mungkin mengalami efek samping lebih serius saat mengonsumsi obat ini.
- Jika Anda juga mengonsumsi irinotekan, kapesitabin, atau doksetaksel, yang merupakan obat-obatan yang digunakan selama pengobatan kanker, Nexavar berpotensi meningkatkan efeknya, dan, khususnya, efek samping obat-obatan antikanker ini.
- Jika Anda sedang meminum antibiotik neomisin, Nexavar mungkin menjadi kurang efektif.
- Jika Anda mengalami gangguan fungsi ginjal. Dokter mungkin akan memantau keseimbangan cairan dan

elektrolit Anda.

Beri tahu dokter jika Anda mengalami kondisi tersebut. Anda mungkin perlu mengobati kondisi tersebut, atau dokter mungkin mengubah dosis Nexavar atau menghentikan pengobatan dengan Nexavar. Lihat juga *Kemungkinan Efek Samping*, bagian 4.

Mengonsumsi obat lainnya
Beberapa obat mungkin menurunkan efektivitas Nexavar atau sebaliknya. Beri tahu dokter atau apoteker jika Anda mengonsumsi salah satu dari yang berikut ini:
- Rifampisin atau neomisin oral, antibiotik
- St. John's wort, obat herbal untuk depresi
- Fenitoin, karbamazepin atau fenobarbital, obat untuk epilepsi dan kondisi lainnya
- Deksametason, kortikosteroid untuk mengobati berbagai kondisi
- Warfarin, atau antikoagulan untuk mencegah penggumpalan darah
- Doksorubisin, doksetaksel, paklitaksel, kaborplatin, dan irinotekan, yang juga merupakan obat untuk kanker
- Neomisin, antibiotik oral, yang digunakan untuk mengobati infeksi.

Beri tahu dokter atau apoteker jika Anda sedang mengonsumsi obat-obatan tersebut atau lainnya (atau mengonsumsi obat apa pun baru-baru ini) – termasuk yang tidak diresepkan dokter.

Kehamilan dan fertilitas
Beritahu dokter Anda jika Anda merasa hamil, mungkin hamil atau berencana untuk hamil dikarenakan Nexavar dilarang dikonsumsi selama kehamilan. Nexavar sebaiknya dikonsumsi saat Anda tidak hamil. Jika masih dalam usia subur, pastikan Anda menggunakan kontrasepsi yang memadai selama pengobatan dan setidaknya selama dua minggu setelah pengobatan selesai. Jika hamil saat sedang menjalani pengobatan dengan Nexavar, hentikan konsumsi Nexavar dan segera beri tahu dokter. Dokter nantinya memutuskan apakah pengobatan perlu dilanjutkan.

Nexavar dapat mengurangi kesuburan pada pria dan wanita. Mintalah saran dari dokter Anda sebelum mengonsumsi Nexavar.

Menyusui
Anda tidak boleh menyusui selama menjalani pengobatan dengan Nexavar. Jika Anda sedang menyusui, maka segera hentikan, karena obat ini dapat memengaruhi pertumbuhan dan perkembangan bayi. Pastikan untuk memberi tahu dokter jika Anda sedang menyusui atau berencana untuk menyusui.

Mengemudi dan mengoperasikan mesin
Belum ada penelitian yang dilakukan mengenai efek Nexavar terhadap kemampuan mengemudi atau mengoperasikan mesin.

3. Cara mengonsumsi Nexavar

Dosis normal Nexavar untuk orang dewasa adalah 2 x tablet 200 mg, diminum dua kali sehari.
Dosis ini setara dengan dosis harian empat tablet atau 800 mg Nexavar per hari.

Minum tablet Nexavar dengan segelas air**,** dengan atau tanpa makanan. Jangan minum obat ini bersama makanan berlemak tinggi, karena dapat membuat Nexavar kurang efektif. Jika Anda berniat makan makanan berlemak tinggi, minum tablet Nexavar 1 jam sebelum makan atau 2 jam setelah makan.

Selalu konsumsi Nexavar sesuai dengan anjuran dokter. Tanyakan kepada dokter atau apoteker jika Anda tidak yakin.

Pastikan Anda minum Nexavar di waktu yang sama tiap harinya agar konsentrasinya stabil dalam aliran darah.

Anda mungkin dianjurkan minum Nexavar sejauh efektif dan Anda tidak mengalami efek samping serius.

Jika Anda mengonsumsi Nexavar melebihi dosis yang dianjurkan

Langsung beri tahu dokter Anda jika Anda (atau orang lain) mengonsumsi Nexavar melebihi dosis yang diresepkan. Mengonsumsi Nexavar berlebihan meningkatkan risiko efek samping atau memperburuk efek samping, khususnya diare dan reaksi pada kulit. Dokter mungkin menganjurkan Anda untuk berhenti mengonsumsi Nexavar.

Jika Anda lupa mengonsumsi Nexavar
Jika melewatkan satu dosis, langsung minum satu dosis saat Anda ingat. Jika sudah mendekati waktu minum dosis berikutnya, minum dosis yang semestinya. Jangan minum dosis ganda untuk mengganti dosis yang terlewat.

4. Kemungkinan efek samping

Seperti obat pada umumnya, Nexavar dapat menimbulkan efek samping pada sebagian orang. Obat ini juga mungkin memengaruhi beberapa tes darah.

Efek samping paling umum
(mungkin dialami oleh lebih dari 1 orang di tiap 10 orang)
- diare
- kelelahan (*fatigue*)
- mual (*nausea*)
- muntah
- kulit kering
- sembelit
- hilang nafsu makan *(*anoreksia*)*
- nyeri (termasuk nyeri mulut, nyeri perut, nyeri tulang, nyeri tumor, dan sakit kepala)
- telapak tangan dan/atau telapak kaki berkeringat atau nyeri atau penebalan kulit di telapak tangan dan/atau telapak kaki (*hand foot skin reaction*)
- kulit kemerahan (*erythema*)
- kulit meradang, kering, atau bersisik yang mengelupas (dermatitis, deskuamasi kulit)
- nyeri sendi atau otot (*artralgia*)
- gatal (*pruritus*) atau ruam
- rambut rontok (*alopecia*)
- perdarahan (termasuk perdarahan pada otak, usus, dan saluran pernapasan (*haemorrhage*)
- tekanan darah tinggi (hipertensi)
- demam
- infeksi
- penurunan berat badan
- perubahan pada tes darah mungkin menunjukkan:
  - kadar fosfor rendah (*hypophosphatemia*)
  - jumlah limfosit rendah (sel darah putih) (*lymphopenia*)
  - kenaikan kadar enzim amilase dan lipase

Efek samping umum
(mungkin dialami oleh 1 di tiap 10 orang dan 1 di tiap 100 orang)
- serangan jantung dan nyeri dada (*infark miokard dan iskemia*)
- gagal jantung kongestif
- sakit menyerupai flu
- peradangan folikel rambut (folikulitis)
- penebalan lapisan luar kulit (hiperkeratosis)
- badan lemas (*asthenia*)
- gangguan pencernaan (*dyspepsia*)
- radang mulut atau mulut kering, lidah nyeri (stomatitis dan peradangan mukosa)
- sulit menelan (*dysphagia*)
- sakit maag (penyakit refluks gastroesofageal)
- suara serak (disfonia*)*
- kelenjar tiroid kurang aktif (hipotiroidisme)
- kanker kulit (*keratoacanthoma*/kanker sel skuamosa kulit)
- nyeri sendi atau otot (atau *myalgia*)
- kontraksi otot yang tiba-tiba dan tidak disengaja (kejang otot)
- kulit meradang, kulit kering, atau kulit bersisik dan mengelupas (*dermatitis, skin desquamation*)
- jerawat
- kesemutan pada jari tangan dan kaki, termasuk rasa nyeri menggelitik atau mati rasa (*neuropati sensorik perifer)*
- merah pada wajah dan sering kali pada area kulit lainnya (kemerahan)
- gangguan indra perasa (*dysgeusia*)
- hidung meler (*rhinorrhea*)
- depresi
- gangguan ereksi (disfungsi ereksi)
- telinga berdenging (*tinnitus*)
- gagal ginjal
- perubahan pada tes darah mungkin menunjukkan:
  jumlah sel darah rendah (sel darah putih, sel darah merah, atau platelet) (leukopenia, neutropenia, anemia, trombositopenia*)*
  - kenaikan sementara enzim di tes hati tertentu (kenaikan sementara kadar transaminase)
  - rendahnya kandungan kalsium dalam darah (*hypocalcaemia*)
  - rendahnya kandungan potasium dalam darah (*hypokalemia*)

- rendahnya kadar natrium dalam darah (*hyponatremia)*
- kandungan protein dalam urine yang sangat tinggi (proteinuria)

Efek samping yang jarang terjadi
(mungkin dialami 1 di tiap 100 orang dan 1 di tiap 1.000 orang)

- peradangan pada dinding perut (gastritis)
- nyeri di bagian perut (abdomen) akibat peradangan pankreas (pankreatitis), kantong empedu (kolesistitis), atau saluran empedu (kolangitis)
- perforasi usus (perforasi gastrointestinal)
- kulit atau mata kuning (*jaundice*) akibat tingginya kadar pigmen empedu (*hyperbilirubinaemia*)
- reaksi alergi (termasuk reaksi pada kulit dan biduran/urtikaria) (reaksi hipersensitivitas)
- reaksi alergi parah dan tiba-tiba (reaksi anafilaktik*)*
- eksim
- erupsi kulit (*erythema multiforme)*
- pertumbuhan kulit terlokalisasi yang jinak *(keratoacanthoma)*
- dehidrasi
- melonjaknya tekanan darah yang menyebabkan sakit kepala, kebingungan, pandangan kabur, mual, muntah, dan kejang (konvulsi) (krisis hipertensi)
- pembengkakan otak bagian belakang yang dapat disembuhkan yang biasanya diasosiasikan dengan tekanan darah tinggi, yang dapat menyebabkan sakit kepala, hilang kesadaran, kejang dan dampak pada penglihatan termasuk hilangnya penglihatan (*leucoencephalopathy* posterior yang dapat disembuhkan)
- peradangan paru (dapat mengakibatkan masalah pernapasan) (insiden penyakit paru interstisial)
- kelenjar tiroid yang terlalu aktif (*hyperthyroidism*)
- payudara membesar (*gynaecomastia)*
    - perubahan pada tes darah mungkin menunjukkan:
    - kenaikan sementara kadar alkali fosfatase dalam darah
    - perubahan hasil tes penggumpalan darah (INR atau protrombin)

Efek samping langka
(mungkin dialami 1 di tiap 1.000 orang dan 1 di tiap 10.000 orang)

- kelainan ritme jantung (ECG) (perpanjangan interval QT)
- kerusakan pada ginjal yang menyebabkan bocornya protein dalam volume tinggi (sindrom nefrotik)
- peradangan hati, yang dapat menyebabkan mual, muntah, nyeri perut, dan *jaundice* (hepatitis yang diinduksi obat)

Efek samping lainnya yang tidak diketahui
(frekuensi kejadiannya tidak bisa ditentukan berdasarkan data yang ada)

- reaksi alergi dengan pembengkakan pada kulit (mis. pada wajah dan lidah) yang dapat mengakibatkan kesulitan bernapas atau menelan (angioedema)
- kondisi kulit parah dengan melepuhnya kulit dan membran mukosa, termasuk terlepasnya kulit di area yang luas *(sindrom Stevens-Johnson* dan nekrolisis epidermal toksik*)*
- ruam seperti terbakar sinar matahari yang mungkin timbul pada kulit yang sebelumnya terpapar radioterapi dan mungkin parah (dermatitis akibat radiasi)
- peradangan pembuluh darah pada kulit yang menimbulkan ruam (vaskulitis leukositoklastik)
- kerusakan otot abnormal yang dapat menimbulkan penyakit ginjal (rabdomiolisis)

Pelaporan dugaan efek samping obat
Jika mengalami efek samping selama dan/atau setelah penggunaan obat, segera konsultasikan ke dokter atau tenaga kesehatan lainnya.
Untuk pelaporan efek samping, silahkan email ke drugsafety.indonesia@bayer.com. Informasi yang disampaikan sangat penting untuk pemantauan manfaat-risiko produk yang berkelanjutan.

5. Cara menyimpan Nexavar

Jauhkan obat ini dari pandangan dan jangkauan anak-anak.

Jangan konsumsi obat ini setelah melewati tanggal kadaluarsa yang tertera di blister dan dus setelah kata EXP. Tanggal kadaluwarsa mengacu pada hari terakhir dari bulan tersebut.

Obat ini tidak memerlukan kondisi penyimpanan khusus apapun.

Jangan membuang obat apapun ke dalam saluran pembuangan air limbah atau sampah rumah tangga. Tanyakan kepada Apoteker bagaimana cara membuang obat yang tidak lagi Anda gunakan. Tindakan-tindakan ini akan membantu melindungi lingkungan.

Jangan disimpan pada suhu lebih dari 30°C.

6. Kemasan dan informasi lainnya

Kandungan Nexavar
- Zat aktifnya adalah sorafenib. Setiap tablet mengandung 274 mg sorafenib tosilat setara dengan 200 mg sorafenib.
- Bahan lainnya adalah:
  - Inti tablet : natrium kroskarmelosa, selulosa mikrokristalin, hipermelosa, natrium laurilsulfat, magnesium stearat.
  - Salut tablet : hipermelosa, makrogol, titanium dioksida (E 171), ferri oksida merah (E 172).

Seperti Apa Nexavar dan isi kemasannya
Tablet salut selaput Nexavar 200 mg berwarna merah dan bulat dengan tanda silang Bayer di satu sisi dan “200” di sisi lainnya.

Kemasan Nexavar
Nexavar tersedia dalam kemasan :

Dus, 6 blister @ 10 tablet salut selaput, No. Reg. DKIXXXXXXXXXXX

Harus dengan resep dokter

Dibuat oleh Patheon France S.A.S., Bourgoin-Jallieu – Prancis

Dikemas dan dirilis oleh Bayer AG, Leverkusen – Jerman

Diimpor oleh PT Bayer Indonesia, Depok – Indonesia