CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

NDA 21-923

Approved Labeling

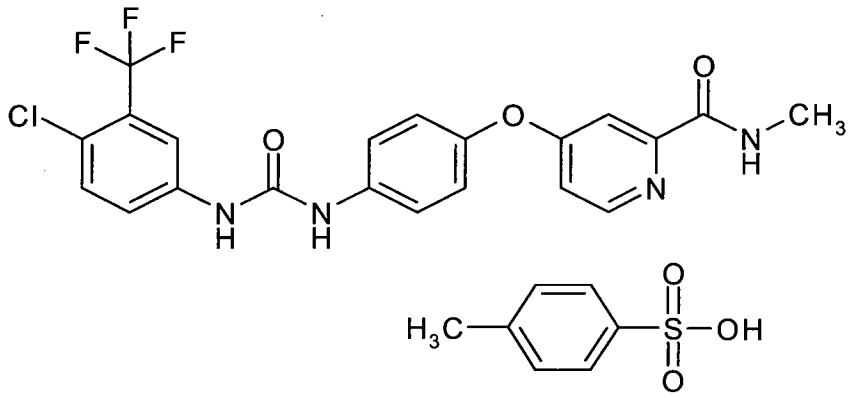
NEXAVAR®

(sorafenib)
tablets 200 mg

DESCRIPTION

NEXAVAR, a multikinase inhibitor targeting several serine/threonine and receptor tyrosine kinases, is the tosylate salt of sorafenib.

Sorafenib tosylate has the chemical name 4-(4-{3-[4-Chloro-3-(trifluoromethyl)phenyl] ureido}phenoxy)-N^2-methylpyridine-2-carboxamide 4-methylbenzenesulfonate and its structural formula is:



Sorafenib tosylate is a white to yellowish or brownish solid with a molecular formula of $C_{21}H_{16}ClF_3N_4O_3$ x $C_7H_8O_3S$ and a molecular weight of 637.0 g/mole. Sorafenib tosylate is practically insoluble in aqueous media, slightly soluble in ethanol and soluble in PEG 400.

Each red, round NEXAVAR film-coated tablet contains sorafenib tosylate (274 mg) equivalent to 200 mg of sorafenib and the following inactive ingredients:

croscarmellose sodium, microcrystalline cellulose, hypromellose, sodium lauryl sulphate, magnesium stearate, polyethylene glycol, titanium dioxide and ferric oxide red.

CLINICAL PHARMACOLOGY

Mechanism of Action

Sorafenib is a multikinase inhibitor that decreases tumor cell proliferation *in vitro*. Sorafenib inhibited tumor growth of the murine renal cell carcinoma, RENCA, and several other human tumor xenografts in athymic mice. A reduction in tumor angiogenesis was seen in some tumor xenograft models. Sorafenib was shown to interact with multiple intracellular (CRAF, BRAF and mutant BRAF) and cell surface kinases (KIT, FLT- 3, VEGFR- 2, VEGFR- 3, and PDGFR- ß). Several of these kinases are thought to be involved in angiogenesis.

Pharmacokinetics

After administration of NEXAVAR tablets, the mean relative bioavailability is 38-49% when compared to an oral solution. The mean elimination half-life of sorafenib is approximately 25-48 hours. Multiple dosing of NEXAVAR 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.

Absorption and Distribution

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

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

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

Metabolism and Elimination

Sorafenib is metabolized primarily in the liver, undergoing oxidative metabolism, mediated by CYP3A4, as well as glucuronidation mediated by UGT1A9.

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 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.

Special Populations

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

Race

Limited pharmacokinetic data on sorafenib 400 mg twice daily in a study in Japanese patients (n=6) showed a 45% lower systemic exposure (mean steady-state AUC) as compared to pooled Phase 1 pharmacokinetic data in Caucasian patients (n=25). The clinical significance of this finding is not known (see **PRECAUTIONS – General -** *Race*).

Pediatric

There are no pharmacokinetic data in pediatric patients.

Hepatic Impairment

Sorafenib is cleared primarily by the liver.

In patients with mild (Child-Pugh A, n=14) or moderate (Child-Pugh B, n=8) hepatic impairment, exposure values were within the range observed in patients without hepatic impairment. The pharmacokinetics of sorafenib have not been studied in patients with severe (Child-Pugh C) hepatic impairment (See **PRECAUTIONS – Patients with Hepatic Impairment** section).

Renal Impairment

In a study of drug disposition after a single oral dose of radiolabeled sorafenib to healthy subjects, 19% of the administered dose of sorafenib was excreted in urine.

In four Phase 1 clinical trials, sorafenib was evaluated in patients with normal renal function (n=71) and in patients with mild renal impairment (CrCl >50–80 mL/min, n=24) or moderate renal impairment (CrCl 30–50 mL/min, n=4). No relationship was observed between renal function and steady-state sorafenib AUC at doses of 400 mg twice daily. The pharmacokinetics of sorafenib have not been studied in patients with severe renal impairment (CrCl <30 ml/min) or in patients undergoing dialysis (see **PRECAUTIONS – Patients with Renal Impairment** section).

Drug-Drug Interactions

CYP3A4 inhibitors: *In vitro* data indicate that sorafenib is metabolized by CYP3A4 and UGT1A9 pathways. Ketoconazole (400 mg), a potent inhibitor of CYP3A4, administered once daily for 7 days did not alter the mean AUC of a single oral 50 mg dose of sorafenib in healthy volunteers. Therefore, sorafenib metabolism is unlikely to be altered by CYP3A4 inhibitors.

CYP isoform-selective substrates: Studies with human liver microsomes demonstrated that sorafenib is a competitive inhibitor of CYP2C19, CYP2D6, and CYP3A4 as indicated by K_i values of 17 μM, 22 μM, and 29 μM, respectively. Administration of NEXAVAR 400 mg twice daily for 28 days did not alter the exposure of concomitantly administered midazolam (CYP3A4 substrate), dextromethorphan (CYP2D6 substrate), and omeprazole (CYP2C19 substrate). This indicates that sorafenib is unlikely to alter the metabolism of substrates of these enzymes *in vivo*.

CYP2C9 substrates: 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 the metabolism of the CYP2C9 substrate warfarin was assessed indirectly by measuring PT-INR. The mean changes from baseline in PT-INR were not higher in NEXAVAR

patients compared to placebo patients, suggesting that sorafenib did not inhibit warfarin metabolism *in vivo* (see **PRECAUTIONS** – *Warfarin Co-administration* section).

CYP3A4 inducers: There is no clinical information on the effect of CYP3A4 inducers on the pharmacokinetics of sorafenib. Substances that are inducers of CYP3A4 activity (e.g. rifampin, St. John's wort, phenytoin, carbamazepine, phenobarbital, and dexamethasone) are expected to increase metabolism of sorafenib and thus decrease sorafenib concentrations.

Combination with other antineoplastic agents: In clinical studies, NEXAVAR has been administered with a variety of other antineoplastic agents at their commonly used dosing regimens, including gemcitabine, oxaliplatin, doxorubicin, and irinotecan. Sorafenib had no effect on the pharmacokinetics of gemcitabine or oxaliplatin. Concomitant treatment with NEXAVAR 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 **PRECAUTIONS – Drug Interactions** sections).

***In vitro* studies**

In vitro studies of enzyme inhibition: 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 is expected to increase when co-administered with NEXAVAR.

Sorafenib inhibits glucuronidation by the UGT1A1 (K_i value: 1 μM) and UGT1A9 pathways (K_i value: 2 μM). Systemic exposure to substrates of UGT1A1 and UGT1A9 may increase when co-administered with NEXAVAR.

***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 or CYP3A4.

CLINICAL STUDIES

The safety and efficacy of NEXAVAR in the treatment of advanced renal cell carcinoma (RCC) were studied in the following 2 randomized controlled clinical trials.

Study 1 was a Phase 3, international, multicenter, randomized, double blind, placebo-controlled trial in patients with advanced renal cell carcinoma who had received one prior systemic therapy. Primary study endpoints included overall survival and progression-free survival (PFS). Tumor response rate was a secondary endpoint. The PFS analysis included 769 patients stratified by MSKCC (Memorial Sloan Kettering Cancer Center) prognostic risk category[1] (low or intermediate) and country and randomized to NEXAVAR 400 mg twice daily (N=384) or to placebo (N=385).

Table 1 summarizes the demographic and disease characteristics of the study population analyzed. Baseline demographics and disease characteristics were well balanced for both treatment groups. The median time from initial diagnosis of RCC to randomization was 1.6 and 1.9 years for the NEXAVAR and placebo groups, respectively.

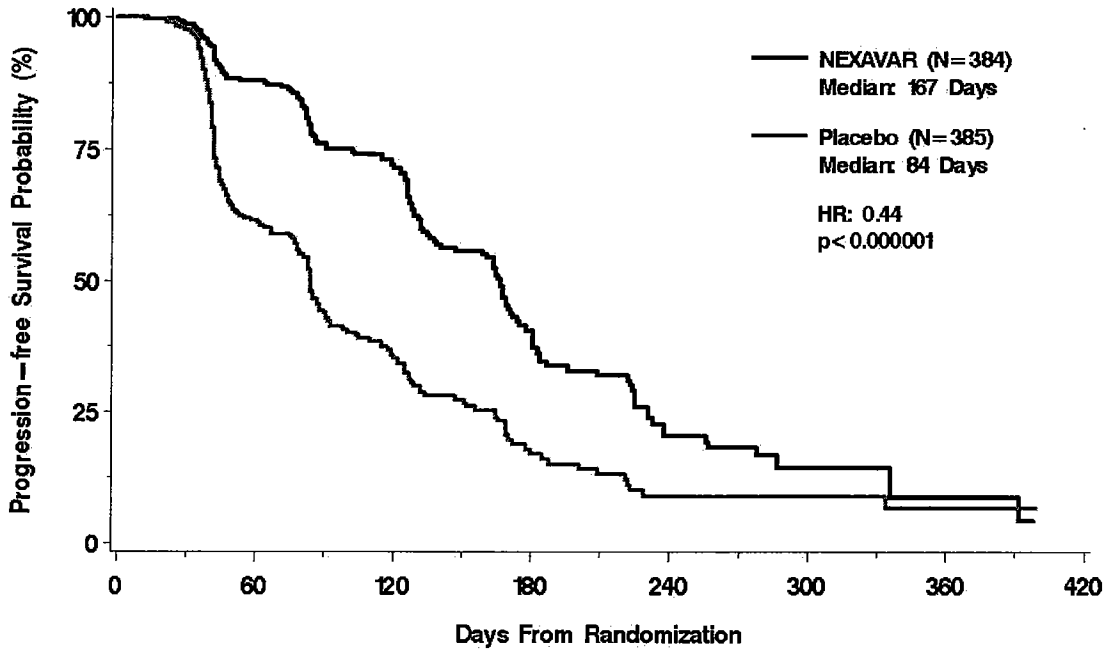
139 **Table 1: Demographic and Disease Characteristics - Study 1**

Characteristics	NEXAVAR N=384 N	(%)	Placebo N=385 n	(%)
Gender				
Male	267	(70)	287	(75)
Female	116	(30)	98	(25)
Race				
White	276	(72)	278	(73)
Black/Asian/ Hispanic/Other	11	(3)	10	(2)
Not reported [a]	97	(25)	97	(25)
Age group				
< 65 years	255	(67)	280	(73)
≥ 65 years	127	(33)	103	(27)
ECOG performance status at baseline				
0	184	(48)	180	(47)
1	191	(50)	201	(52)
2	6	(2)	1	(<1)
Not reported	3	(<1)	3	(<1)
MSKCC prognostic risk category[1]				
Low	200	(52)	194	(50)
Intermediate	184	(48)	191	(50)
Prior IL-2 and/or interferon				
Yes	319	(83)	313	(81)
No	65	(17)	72	(19)

a. Race was not collected from the 186 patients enrolled in France due to local regulations. In 8 other patients, race was not available at the time of analysis.

Progression-free survival, defined as the time from randomization to progression or death from any cause, whichever occurred earlier, was evaluated by blinded independent radiological review using RECIST criteria. Figure 1 depicts Kaplan-Meier curves for PFS. The PFS analysis was based on a two-sided Log-Rank test stratified by MSKCC prognostic risk category[1] and country.

Figure 1: Kaplan-Meier Curves for Progression-free Survival – Study 1



NOTE: HR is from Cox regression model with the following covariates: MSKCC prognostic risk category[1] and country. P-value is from two-sided Log-Rank test stratified by MSKCC prognostic risk category[1] and country.

The median PFS for patients randomized to NEXAVAR was 167 days compared to 84 days for patients randomized to placebo. The estimated hazard ratio (risk of progression with NEXAVAR compared to placebo) was 0.44 (95% CI: 0.35, 0.55).

A series of patient subsets were examined in exploratory univariate analyses of PFS. 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.

Tumor response was determined by independent radiological review according to RECIST criteria. Overall, of 672 patients who were evaluable for response, 7 (2%) NEXAVAR patients and 0 (0%) placebo patients had a confirmed partial response. Thus the gain in PFS in NEXAVAR-treated patients primarily reflects the stable disease population.

At the time of a planned interim survival analysis, based on 220 deaths, overall survival was longer for NEXAVAR than placebo with a hazard ratio (NEXAVAR over placebo) of 0.72. This analysis did not meet the prespecified criteria for statistical significance. Additional analyses are planned as the survival data mature.

Study 2 was a Phase 2 randomized discontinuation trial in patients with metastatic malignancies, including RCC. The primary endpoint was the percentage of randomized patients remaining progression-free at 24 weeks. All patients received NEXAVAR for the first 12 weeks. Radiologic assessment was repeated at week 12. Patients with <25% change in bi-dimensional tumor measurements from baseline were randomized to NEXAVAR or placebo for a further 12 weeks. Patients who were randomized to placebo were permitted to cross over to open-label NEXAVAR upon progression. Patients with tumor shrinkage ≥25% continued NEXAVAR, whereas patients with tumor growth ≥25% discontinued treatment.

Two hundred and two patients with advanced RCC were enrolled into Study 2, including patients who had received no prior therapy and patients with tumor histology other than clear cell carcinoma. After the initial 12 weeks of NEXAVAR therapy, 79 RCC patients continued on open-label NEXAVAR, and 65 patients were randomized to NEXAVAR or placebo. After an additional 12 weeks, at week 24, for the 65 randomized patients, the progression-free rate was significantly higher in patients randomized to NEXAVAR (16/32, 50%) than in patients randomized to placebo (6/33, 18%) (p=0.0077). 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).

INDICATIONS AND USAGE

NEXAVAR is indicated for the treatment of patients with advanced renal cell carcinoma.

CONTRAINDICATIONS

NEXAVAR is contraindicated in patients with known severe hypersensitivity to sorafenib or any other component of NEXAVAR.

WARNINGS

Pregnancy Category D

In rats and rabbits, sorafenib has been shown to be teratogenic and to induce embryo-fetal toxicity (including increased post-implantation loss, resorptions, skeletal retardations, and retarded fetal weight). The effects occurred at doses considerably below the recommended human dose of 400 mg twice daily (approximately 500 mg/m^2/day on a body surface area basis). Adverse intrauterine development effects were seen at doses ≥ 1.2 mg/m^2/day in rats and 3.6 mg/m^2/day in rabbits (approximately 0.008 times the AUC seen in cancer patients at the recommended human dose). A NOAEL (no observed adverse effect level) was not defined for either species, since lower doses were not tested.

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. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus (see **PRECAUTIONS – Information for Patients** section).

There are no adequate and well-controlled studies in pregnant women using NEXAVAR. Women of childbearing potential should be advised to avoid becoming pregnant while on NEXAVAR. NEXAVAR should be used during pregnancy only if the potential benefits justify the potential risks to the fetus (see **PRECAUTIONS – Information for Patients** section).

PRECAUTIONS

General

Dermatologic Toxicities: Hand-foot skin reaction and rash represent the most common adverse events attributed to NEXAVAR. Analysis of cumulative event rates from Study 1 suggest that rash and hand-foot skin reaction are usually CTCAE Grade 1 and 2 and generally appear during the first six weeks of treatment with NEXAVAR. Management of dermatologic toxicities may include topical therapies for symptomatic relief, temporary treatment interruption and/or dose modification of NEXAVAR, or in severe or persistent cases, permanent discontinuation of NEXAVAR. Permanent discontinuation of therapy due to hand-foot skin reaction occurred in 3 of 451 NEXAVAR patients.

Hypertension: In Study 1, treatment-emergent hypertension was reported in approximately 16.9% of NEXAVAR-treated patients and 1.8% of patients in the placebo group. Hypertension was usually mild to moderate, occurred early in the course of treatment, and was managed with standard antihypertensive therapy. Blood pressure should be monitored weekly during the first 6 weeks of NEXAVAR therapy and thereafter monitored and treated, if required, in accordance with standard medical practice. In cases of severe or persistent hypertension, despite institution of antihypertensive therapy, temporary or permanent discontinuation of NEXAVAR should be considered. Permanent discontinuation due to hypertension occurred in 1 of 451 NEXAVAR patients.

Hemorrhage: An increased risk of bleeding may occur following NEXAVAR administration. In Study 1, bleeding regardless of causality was reported in 15.3% of patients in the NEXAVAR group and 8.2% of patients in the placebo group. The incidence of CTCAE Grade 3 and 4 bleeding events was 2% and 0%, respectively, in NEXAVAR patients, and 1.3% and 0.2%, respectively, in placebo patients. There was one fatal hemorrhage in each treatment group in Study 1. If any bleeding event necessitates medical intervention, permanent discontinuation of NEXAVAR should be considered.

Cardiac Ischemia and/or Infarction: In Study 1, the incidence of treatment-emergent cardiac ischemia/infarction events was higher in the NEXAVAR group (2.9%) compared with the placebo group (0.4%). Patients with unstable coronary artery disease or recent myocardial

infarction were excluded from this study. Temporary or permanent discontinuation of NEXAVAR should be considered in patients who develop cardiac ischemia and/or infarction.

Race: Limited pharmacokinetic data on sorafenib 400 mg twice daily in a study in Japanese patients (n=6) showed a 45% lower systemic exposure (mean steady-state AUC) as compared to pooled Phase 1 pharmacokinetic data in Caucasian patients (n=25). The clinical significance of this finding is not known.

Warfarin Co-administration: Infrequent bleeding events or elevations in the International Normalized Ratio (INR) have been reported in some patients taking warfarin while on NEXAVAR therapy. Patients taking concomitant warfarin should be monitored regularly for changes in prothrombin time, INR or clinical bleeding episodes.

Wound Healing Complications: No formal studies of the effect of NEXAVAR on wound healing have been conducted. Temporary interruption of NEXAVAR therapy is recommended in patients undergoing major surgical procedures. There is limited clinical experience regarding the timing of reinitiation of NEXAVAR therapy following major surgical intervention. Therefore, the decision to resume NEXAVAR therapy following a major surgical intervention should be based on clinical judgment of adequate wound healing.

Drug Interactions

Caution is recommended when administering NEXAVAR with compounds that are metabolized/eliminated predominantly by the UGT1A1 pathway (e.g. irinotecan) (see **CLINICAL PHARMACOLOGY – Drug-Drug Interactions** section).

Concomitant treatment with NEXAVAR resulted in a 21% increase in the AUC of doxorubicin. Caution is recommended when administering doxorubicin with NEXAVAR.

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 is expected to increase when co-administered with NEXAVAR. Caution is recommended when administering substrates of CYP2B6 and CYP2C8 with NEXAVAR.

Patients with Hepatic Impairment

In vitro and *in vivo* data indicate that sorafenib is primarily metabolized by the liver. Systemic exposure and safety data were comparable in patients with Child-Pugh A and B hepatic impairment. NEXAVAR has not been studied in patients with Child-Pugh C hepatic impairment. No dose adjustment is necessary when administering NEXAVAR to patients with Child-Pugh A and B hepatic impairment (see **CLINICAL PHARMACOLOGY – Hepatic Impairment** section).

Patients with Renal Impairment

NEXAVAR has not been studied in patients with severe renal impairment (CrCl <30 mL/min) or in patients undergoing dialysis.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity studies have not been performed with sorafenib.

Sorafenib was clastogenic when tested in an *in vitro* mammalian cell assay (Chinese Hamster Ovary) in the presence of metabolic activation. Sorafenib was not mutagenic in the *in vitro* Ames bacterial cell assay or clastogenic in an *in vivo* mouse micronucleus assay. One intermediate in the manufacturing process, which is also present in the final drug substance (<0.15%), was positive for mutagenesis in an *in vitro* bacterial cell assay (Ames test) when tested independently.

No specific studies with sorafenib have been conducted in animals to evaluate the effect on fertility. However, results from the repeat-dose toxicity studies suggest there is a potential for sorafenib to impair reproductive performance and fertility. Multiple adverse effects were observed in male and female reproductive organs, with the rat being more susceptible than mice or dogs. Typical changes in rats consisted of testicular atrophy or degeneration, degeneration of epididymis, prostate, and seminal vesicles, central necrosis of the corpora lutea and arrested follicular development. Sorafenib-related effects on the reproductive organs of rats were manifested at daily oral doses ≥30 mg/m^2 (approximately 0.5 times the AUC in cancer patients at the recommended human dose). Dogs showed tubular degeneration in the testes at 600 mg/m^2/day (approximately 0.3 times the AUC at the recommended human dose) and oligospermia at 1200 mg/m^2/day of sorafenib.

Adequate contraception should be used during therapy and for at least 2 weeks after completing therapy.

Pregnancy Category D (see WARNINGS)

Nursing Mothers

It is not known whether sorafenib is excreted in human milk. Following administration of ^{14}C-sorafenib to lactating Wistar rats, approximately 27% of the radioactivity was secreted into the milk. The milk to plasma AUC ratio was approximately 5:1.

Because many drugs are excreted in human milk and because the effects of sorafenib on infants have not been studied, women should be advised against breast-feeding while receiving NEXAVAR.

Pediatric Use

The safety and effectiveness of NEXAVAR in pediatric patients have not been studied.

Repeat dosing of sorafenib to young and growing dogs resulted in irregular thickening of the femoral growth plate at daily sorafenib doses ≥600 mg/m^2 (approximately 0.3 times the AUC at the recommended human dose), hypocellularity of the bone marrow adjoining the growth plate at 200 mg/m^2/day (approximately 0.1 times the AUC at the recommended human dose), and alterations of the dentin composition at 600 mg/m^2/day. Similar effects were not observed in adult dogs when dosed for 4 weeks or less.

Geriatric Use

In total, 32% of RCC patients treated with NEXAVAR were age 65 years or older, and 4% were 75 and older. No differences in safety or efficacy were observed between older and younger patients, and other reported clinical experience has not identified differences in

responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

Information for Patients (see Patient Information About: NEXAVAR)

Physicians should inform female patients that NEXAVAR may cause birth defects or fetal loss and that they should not become pregnant during treatment with NEXAVAR and for at least 2 weeks after stopping treatment. Both male and female patients should be counseled to use effective birth control during treatment with NEXAVAR and for at least 2 weeks after stopping treatment. Female patients should also be advised against breast-feeding while receiving NEXAVAR.

Patients should be advised of the possible occurrence of hand-foot skin reaction and rash during NEXAVAR treatment and appropriate countermeasures. Patients should be informed that hypertension may develop during NEXAVAR treatment, especially during the first six weeks of therapy, and that blood pressure should be monitored regularly during treatment.

Physicians should inform patients that NEXAVAR may increase the risk of bleeding and that they should promptly report any episodes of bleeding.

Physicians should also discuss with patients that cardiac ischemia and/or infarction has been reported during NEXAVAR treatment, and that they should immediately report any episodes of chest pain or other symptoms of cardiac ischemia and/or infarction.

ADVERSE REACTIONS

Safety evaluation of NEXAVAR is based on 1286 cancer patients who received NEXAVAR as monotherapy and 165 patients who received NEXAVAR concurrently with chemotherapy. A total of 346 patients were exposed to NEXAVAR monotherapy for greater than 6 months. A total of 664 RCC patients received NEXAVAR monotherapy, of whom 215 were treated for at least 6 months.

Table 2 shows the percent of patients experiencing treatment-emergent adverse events that were reported in at least 10% of patients who received NEXAVAR in Study 1. CTCAE Grade 3 treatment-emergent adverse events were reported in 31% of patients receiving NEXAVAR compared to 22% of patients receiving placebo. CTCAE Grade 4 treatment-emergent adverse events were reported in 7% of patients receiving NEXAVAR compared to 6% of patients receiving placebo.

Table 2: Treatment-Emergent Adverse Events Reported in at Least 10% of NEXAVAR-Treated Patients – Study 1

Adverse Event NCI-CTCAE v3 Category/Term	NEXAVAR N=451			Placebo N=451		
	All Grades %	Grade 3 %	Grade 4 %	All Grades %	Grade 3 %	Grade 4 %
Any Event	95	31	7	86	22	6
Cardiovascular, General						
Hypertension	17	3	<1	2	<1	0
Constitutional symptoms						
Fatigue	37	5	<1	28	3	<1
Weight loss	10	<1	0	6	0	0
Dermatology/skin						
Rash/desquamation	40	<1	0	16	<1	0
Hand -foot skin reaction	30	6	0	7	0	0
Alopecia	27	<1	0	3	0	0
Pruritus	19	<1	0	6	0	0
Dry skin	11	0	0	4	0	0
Gastrointestinal symptoms						
Diarrhea	43	2	0	13	<1	0
Nausea	23	<1	0	19	<1	0
Anorexia	16	<1	0	13	1	0
Vomiting	16	<1	0	12	1	0
Constipation	15	<1	0	11	<1	0
Hemorrhage/bleeding						
Hemorrhage – all sites	15	2	0	8	1	<1
Neurology						
Neuropathy-sensory	13	<1	0	6	<1	0
Pain						
Pain, abdomen	11	2	0	9	2	0
Pain, joint	10	2	0	6	<1	0
Pain, headache	10	<1	0	6	<1	0
Pulmonary						
Dyspnea	14	3	<1	12	2	<1
Cough	13	<1	0	14	<1	0

The rate of adverse events (including events associated with progressive disease) resulting in permanent discontinuation was similar in both the NEXAVAR and placebo groups (10% of NEXAVAR patients and 8% of placebo patients).

Safety was also assessed in a Phase 2 study pool comprised of 638 NEXAVAR-treated patients, including 202 patients with RCC, 137 patients with hepatocellular carcinoma, and 299 patients with other cancers. The most common drug-related adverse events reported in

NEXAVAR-treated patients in this pool were rash (38%), diarrhea (37%), hand-foot skin reaction (35%), and fatigue (33%). The respective rates of CTC (v 2.0) Grade 3 and 4 drug-related adverse events in NEXAVAR-treated patients were 37% and 3%, respectively.

Additional Data from Multiple Clinical Trials

The following additional drug-related adverse events and laboratory abnormalities were reported from clinical trials of NEXAVAR in 1286 cancer patients who received NEXAVAR as monotherapy (*very common* 10% or greater, *common* 1 to less than 10%, *uncommon* 0.1% to less than 1%):

Cardiovascular: *Uncommon:* hypertensive crisis, myocardial ischemia and/or infarction

Dermatologic: *Very common:* erythema *Common:* exfoliative dermatitis, acne, flushing *Uncommon:* folliculitis, eczema, erythema multiforme

Digestive: *Very common:* increased lipase, increased amylase *Common:* mucositis, stomatitis (including dry mouth and glossodynia), dyspepsia, dysphagia *Uncommon:* pancreatitis, gastrointestinal reflux, gastritis

Note that elevations in lipase are very common (41%, see below); a diagnosis of pancreatitis should not be made solely on the basis of abnormal laboratory values

General Disorders: *Very common:* asthenia, pain (including mouth pain, bone pain, and muscle pain) *Common:* decreased appetite, influenza-like illness, pyrexia *Uncommon:* infection

Hematologic: *Very common:* leukopenia, lymphopenia *Common:* anemia, neutropenia, thrombocytopenia *Uncommon:* INR abnormal

Hypersensitivity: *Uncommon:* hypersensitivity reactions (including skin reactions and urticaria)

Metabolic and Nutritional: *Very common:* hypophosphatemia *Common:* transient increases in transaminases *Uncommon:* dehydration, hyponatremia, transient increases in alkaline phosphatase, increased bilirubin (including jaundice), hypothyroidism

Musculoskeletal: *Common:* arthralgia, myalgia

Nervous System and Psychiatric: *Common:* depression *Uncommon:* tinnitus

Reproductive: *Common:* erectile dysfunction *Uncommon:* gynecomastia

Respiratory: *Common:* hoarseness *Uncommon:* rhinorrhea

In addition, the following medically significant adverse events were reported infrequently during clinical trials of NEXAVAR: cerebral hemorrhage, transient ischemic attack, cardiac failure, arrhythmia, thromboembolism, acute renal failure. For these events, the causal relationship to NEXAVAR has not been established.

LABORATORY ABNORMALITIES

The following laboratory abnormalities were observed in Study 1:

Hypophosphatemia was a common laboratory finding, observed in 45% of NEXAVAR-treated patients compared to 11% of placebo patients. CTCAE Grade 3 hypophosphatemia (1-2 mg/dL) occurred in 13% of NEXAVAR-treated patients and 3% of patients in the placebo group. There were no cases of CTCAE Grade 4 hypophosphatemia (<1 mg/dL) reported in either NEXAVAR or placebo patients. The etiology of hypophosphatemia associated with NEXAVAR is not known.

Elevated lipase was observed in 41% of patients treated with NEXAVAR compared to 30% of patients in the placebo group. CTCAE Grade 3 or 4 lipase elevations occurred in 12% of patients in the NEXAVAR group compared to 7% of patients in the placebo group. Elevated amylase was observed in 30% of patients treated with NEXAVAR compared to 23% of patients in the placebo group. CTCAE Grade 3 or 4 amylase elevations were reported in 1% of patients in the NEXAVAR group compared to 3% of patients in the placebo 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 3 of 451 NEXAVAR-treated patients (one CTCAE Grade 2 and two Grade 4) and 1 of 451 patients (CTCAE Grade 2) in the placebo group.

Lymphopenia was observed in 23% of NEXAVAR-treated patients and 13% of placebo patients. CTCAE Grade 3 or 4 lymphopenia was reported in 13% of NEXAVAR-treated patients and 7% of placebo patients. Neutropenia was observed in 18% of NEXAVAR-treated patients and 10% of placebo patients. CTCAE Grade 3 or 4 neutropenia was reported in 5% of NEXAVAR-treated patients and 2% of placebo patients.

Anemia was observed in 44% of NEXAVAR-treated patients and 49% of placebo patients. CTCAE Grade 3 or 4 anemia was reported in 2% of NEXAVAR-treated patients and 4% of placebo patients.

Thrombocytopenia was observed in 12% of NEXAVAR-treated patients and 5% of placebo patients. CTCAE Grade 3 or 4 thrombocytopenia was reported in 1% of NEXAVAR-treated patients and 0% of placebo patients.

OVERDOSAGE

There is no specific treatment for NEXAVAR overdose.

The highest dose of NEXAVAR studied clinically is 800 mg twice daily. The adverse reactions observed at this dose were primarily diarrhea and dermatologic events. No information is available on symptoms of acute overdose in animals because of the saturation of absorption in oral acute toxicity studies conducted in animals.

In cases of suspected overdose, NEXAVAR should be withheld and supportive care instituted.

DOSAGE AND ADMINISTRATION

The recommended daily dose of NEXAVAR is 400 mg (2 x 200 mg tablets) taken twice daily, without food (at least 1 hour before or 2 hours after eating). Treatment should continue

until the patient is no longer clinically benefiting from therapy or until unacceptable toxicity occurs.

Management of suspected adverse drug reactions may require temporary interruption and/or dose reduction of NEXAVAR therapy. When dose reduction is necessary, the NEXAVAR dose may be reduced to 400 mg once daily. If additional dose reduction is required, NEXAVAR may be reduced to a single 400 mg dose every other day (see **PRECAUTIONS**).

Suggested dose modifications for skin toxicity are outlined in Table 3.

Table 3: Suggested Dose Modifications for Skin Toxicity

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

No dose adjustment is required on the basis of patient age, gender, body weight, or in patients with Child-Pugh A or B hepatic impairment. NEXAVAR has not been studied in patients with Child-Pugh C hepatic impairment or severe renal impairment including dialysis patients (see **CLINICAL PHARMACOLOGY – Special Populations - Hepatic Impairment, Renal Impairment, and PRECAUTIONS** sections).

HOW SUPPLIED

NEXAVAR tablets are supplied as round, biconvex, red film-coated tablets, debossed with the "Bayer cross" on one side and "200" on the other side, each containing sorafenib tosylate equivalent to 200 mg of sorafenib.

Bottles of 120 tablets NDC 0026-8488-58

Storage

Store at 25°C (77°F); excursions permitted to 15-30°C (59–86°F) (see USP controlled room temperature). Store in a dry place.

REFERENCES

1. Motzer RJ, Bacik J, Schwartz LH, Reuter V, Russo P, Marion S, et al. Prognostic factors for survival in previously treated patients with metastatic renal cell carcinoma. *J Clin Oncol* 2004;223:454-63.

Rx Only

Manufactured by:
Bayer HealthCare
Bayer HealthCare AG,
Leverkusen, Germany

Manufactured for:
Bayer Pharmaceuticals Corporation,
400 Morgan Lane, West Haven, CT 06516
Onyx Pharmaceuticals, Inc.,
2100 Powell Street, Emeryville, CA 94608

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461 Revision number 12/05 12875

 Printed in U.S.A.

Patient Information About:

NEXAVAR® (NEX-A-VAR)
(sorafenib)
tablets 200 mg

Read the Patient Information that comes with NEXAVAR before you start taking it and each time you get a refill. There may be new information. This leaflet does not take the place of talking with your doctor or healthcare professional about your medical condition or your treatment.

What is the most important information I should know about NEXAVAR?

NEXAVAR may cause birth defects or death of an unborn baby.

- Women should not get pregnant during treatment with NEXAVAR and for at least 2 weeks after stopping treatment.
- Men and women should use effective birth control during treatment with NEXAVAR and for at least 2 weeks after stopping treatment.

Call your doctor right away if you become pregnant during treatment with NEXAVAR.

What is NEXAVAR?

NEXAVAR is an anticancer medicine to treat adults with kidney cancer called advanced renal cell carcinoma.

NEXAVAR has not been studied in children.

Who should not take NEXAVAR?

- **Do not take NEXAVAR if you are allergic to anything in it.** See the end of this leaflet for a complete list of ingredients.

What should I tell my doctor before starting NEXAVAR?

Tell your doctor about all of your health conditions, including if you:

- **have kidney problems in addition to kidney cancer**
- **have liver problems**
- **have high blood pressure**
- **have bleeding problems**
- **have heart problems or chest pain**

- **are pregnant.** See "What is the most important information I should know about NEXAVAR?"

- **are breast-feeding.** NEXAVAR may harm your baby.

Tell your doctor about all the medicines you take including prescription and non-prescription medicines, vitamins and herbal supplements. NEXAVAR and certain other medicines can interact with each other and cause serious side effects. **Especially, tell your doctor if you take warfarin (Coumadin®)*.**

Know the medicines you take. Keep a list of them to show to your doctor and pharmacist. Do not take other medicines with NEXAVAR until you have talked with your doctor.

If you need to have a surgical or dental procedure, tell your doctor that you are taking NEXAVAR.

How do I take NEXAVAR?

- Take NEXAVAR exactly as prescribed. You will stay on NEXAVAR as long as your doctor thinks it is helping you.

- The usual dose of NEXAVAR is 2 tablets taken twice a day (for a total of 4 tablets per day). Your doctor may adjust your dose during treatment or stop treatment for some time if you have side effects.

- Swallow NEXAVAR tablets whole with water.

- Take NEXAVAR on an empty stomach (at least 1 hour before or 2 hours after a meal).

- If you miss a dose of NEXAVAR, skip the missed dose, and take your next dose at your regular time. Do **not** double your dose of NEXAVAR. Call your doctor right away if you take too much NEXAVAR.

What are possible side effects of NEXAVAR?

NEXAVAR may cause serious side effects, including:

- **birth defects or death of an unborn baby.** See "What is the most important information I should know about NEXAVAR?"

- **a skin problem called hand-foot skin reaction.** This causes redness, pain, swelling, or blisters on the palms of your hands or soles of your feet. If you get this side effect, your doctor may adjust your dose or stop treatment for some time.

- **high blood pressure.** Your blood pressure should be checked weekly during the first 6 weeks of starting NEXAVAR. High blood pressure should be monitored and treated during treatment with NEXAVAR.

- **heart problems**. Talk to your doctor about these potential problems.

- **bleeding problems.** NEXAVAR may increase your chance of bleeding.

Other side effects with NEXAVAR may include:

- rash, redness or itching of your skin
- hair thinning or patchy hair loss
- diarrhea (frequent and/or loose bowel movements)
- nausea and/or vomiting
- mouth sores
- weakness
- loss of appetite
- numbness, tingling or pain in your hands and feet

Talk with your doctor about ways to manage any side effects.

These are not all the side effects with NEXAVAR. Ask your doctor or pharmacist for more information.

How should I store NEXAVAR?

- Store NEXAVAR tablets at room temperature between 59° - 86° F (15° to 30° C), in a dry place.

- **Keep NEXAVAR and all medicines out of the reach of children.**

General information about NEXAVAR

Medicines are sometimes prescribed for purposes other than those listed in the patient information leaflet. Do not use NEXAVAR for a condition for which it is not prescribed. Do not share your medicine with other people even if they have the same symptoms you have. It may harm them.

This leaflet summarizes the most important information about NEXAVAR. If you would like more information, talk with your doctor. You can ask your doctor or pharmacist for information about NEXAVAR that is written for healthcare professionals.

Website and toll free number:

www.nexavar.com

555 1-866-NEXAVAR (1-866-639-2827)

556

557 **What are the ingredients in NEXAVAR?**

558 **Active Ingredient:** sorafenib tosylate

559 **Inactive Ingredients:** croscarmellose sodium, microcrystalline cellulose, hypromellose,
560 sodium lauryl sulphate, magnesium stearate, polyethylene glycol, titanium dioxide and
561 ferric oxide red.

562 **Rx Only**

563 *Coumadin (warfarin sodium) is a trademark of Bristol-Myers Squibb Company

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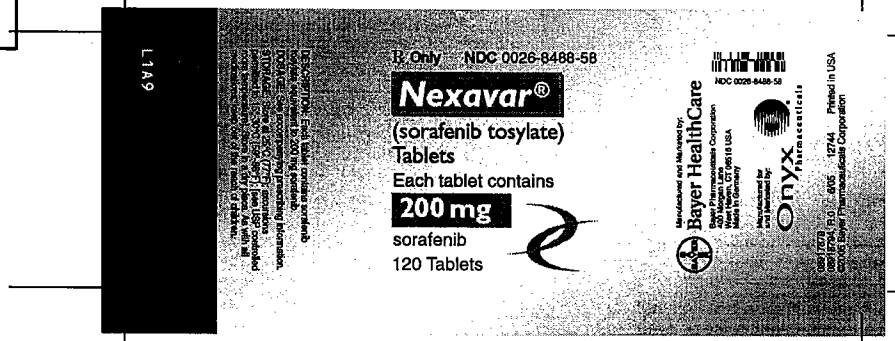
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Tablets
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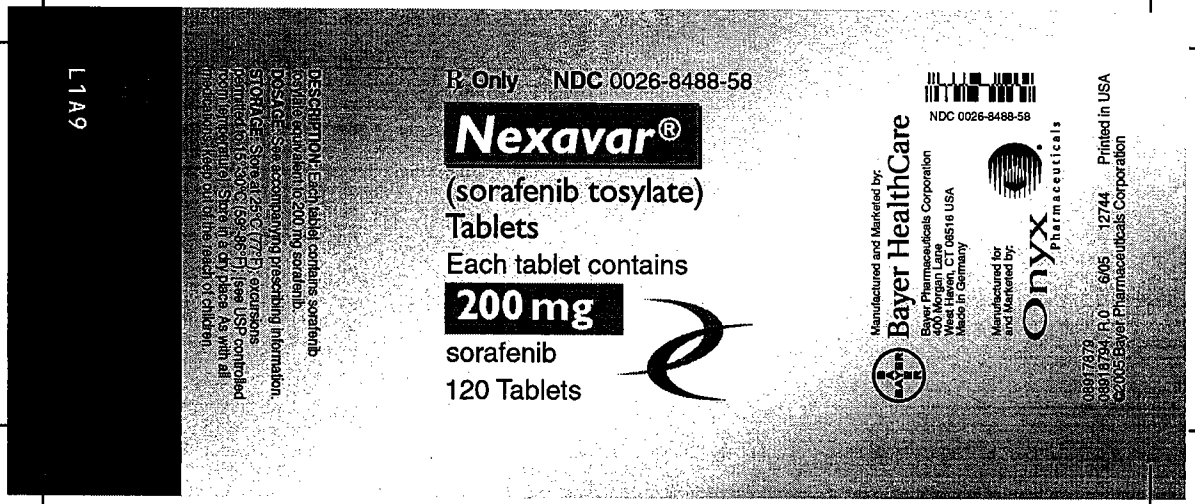
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