HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use NEXAVAR safely and effectively.

See full prescribing information for NEXAVAR.

NEXAVAR (sorafenib) tablets, oral

Initial U.S. Approval: 2005

---------- **INDICATIONS AND USAGE**----------

NEXAVAR is a kinase inhibitor indicated for the treatment of

- Unresectable hepatocellular carcinoma (1.1)
- Advanced renal cell carcinoma (1.2)

----------**DOSAGE AND ADMINISTRATION**----------

- 400 mg (2 tablets) orally twice daily without food. (2)
- Treatment interruption and/or dose reduction may be needed to manage suspected adverse drug reactions. Dose may be reduced to 400 mg once daily or to 400 mg every other day. (2)

---------- **DOSAGE FORMS AND STRENGTHS**----------

200 mg Tablets (3)

---------- **CONTRAINDICATIONS** ----------

- NEXAVAR is contraindicated in patients with known severe hypersensitivity to sorafenib or any other component of NEXAVAR. (4)
- NEXAVAR in combination with carboplatin and paclitaxel is contraindicated in patients with squamous cell lung cancer. (4)

---------- **WARNINGS AND PRECAUTIONS**----------

- Cardiac ischemia and/or infarction may occur. Consider temporary or permanent discontinuation of NEXAVAR. (5.1)
- Bleeding may occur. If bleeding necessitates medical intervention, consider discontinuation of NEXAVAR. (5.2)
- Hypertension usually occurred early in the course of treatment and was managed with antihypertensive therapy. Monitor blood pressure weekly during the first 6 weeks and periodically thereafter and treat, as required. (5.3)
- Hand-foot skin reaction and rash are common. Management may include topical therapies for symptomatic relief, temporary treatment interruption and/or dose modification, or in severe or persistent cases, permanent discontinuation. Stevens-Johnson syndrome and toxic epidermal necrolysis have also occurred. Discontinue if suspected. (5.4)
- Gastrointestinal perforation is an uncommon adverse reaction. In the event of a gastrointestinal perforation, NEXAVAR should be discontinued. (5.5)
- Temporary interruption of NEXAVAR is recommended in patients undergoing major surgical procedures. (5.7)
- QT Prolongation: Monitor for prolonged QT intervals in patients with congestive heart failure, bradyarrhythmias, drugs known to prolong the QT interval, and electrolyte abnormalities. Avoid in patients with congenital long QT syndrome. (5.9, 12.2)
- Drug-induced hepatitis characterized by a hepatocellular pattern may result in hepatic failure and death. Monitor liver function tests regularly and discontinue if there is no alternative explanation for transaminase elevations. (5.10)
- NEXAVAR may cause fetal harm when administered to a pregnant woman. Advise women of childbearing potential to avoid becoming pregnant while on NEXAVAR. (5.11, 8.1)

---------- **ADVERSE REACTIONS** ----------

The most common adverse reactions (≥20%), which were considered to be related to NEXAVAR, are fatigue, weight loss, rash/desquamation, hand-foot skin reaction, alopecia, diarrhea, anorexia, nausea and abdominal pain. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Bayer HealthCare Pharmaceuticals Inc. at 1-888-842-2937, or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

---------- **DRUG INTERACTIONS**----------

- CYP3A4 inducers: Can increase the metabolism of sorafenib and decrease the AUC of sorafenib. (2, 7.1)

---------- **USE IN SPECIFIC POPULATIONS** ----------

- Hepatic impairment: No dose adjustment is necessary for patients with mild (Child-Pugh A) or moderate (Child-Pugh B) hepatic impairment. NEXAVAR has not been studied in patients with severe (Child-Pugh C) hepatic impairment. (8.6)
- Renal impairment: No dose adjustment is necessary for patients with mild (CrCl 50-80 mL/min), moderate (CrCl 30 - <50 mL/min), or severe (CrCl < 30 mL/min) renal impairment. NEXAVAR has not been studied in patients who are on dialysis. (8.7)

See 17 for PATIENT COUNSELING INFORMATION and FDA-Approved Patient Labeling.

Revised: 10/2013

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Hepatocellular Carcinoma

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

1.2 Renal Cell Carcinoma

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

2 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 a meal). 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. 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 Warnings and Precautions (5)]*.

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

Table 1: 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, or body weight.

Concomitant strong CYP3A4 inducers: Avoid concomitant use of strong CYP3A4 inducers (such as, carbamazepine, dexamethasone, phenobarbital, phenytoin, rifampin, rifabutin, St. John's wort), when possible, because inducers can decrease the systemic exposure to sorafenib *[see Drug Interactions (7.1)]*.

3 DOSAGE FORMS AND STRENGTHS

Tablets containing sorafenib tosylate (274 mg) equivalent to 200 mg of sorafenib.

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

4 CONTRAINDICATIONS

- NEXAVAR is contraindicated in patients with known severe hypersensitivity to sorafenib or any other component of NEXAVAR.
- NEXAVAR in combination with carboplatin and paclitaxel is contraindicated in patients with squamous cell lung cancer *[see Warnings and Precautions (5.8)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Risk of Cardiac Ischemia and/or Infarction

In the HCC study, the incidence of cardiac ischemia/infarction was 2.7% in NEXAVAR-treated patients compared with 1.3% in the placebo-treated group and in RCC Study 1, the incidence of cardiac ischemia/infarction was higher in the NEXAVAR-treated group (2.9%) compared with the placebo-treated 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.

5.2 Risk of Hemorrhage

An increased risk of bleeding may occur following NEXAVAR administration. In the HCC study, an excess of bleeding regardless of causality was not apparent and the rate of bleeding from esophageal varices was 2.4% in NEXAVAR-treated patients and 4% in placebo-treated patients. Bleeding with a fatal outcome from any site was reported in 2.4% of NEXAVAR-treated patients and 4% in placebo-treated patients. In RCC Study 1, bleeding regardless of causality was reported in 15.3% of patients in the NEXAVAR-treated group and 8.2% of patients in the placebo-treated group. The incidence of CTCAE Grade 3 and 4 bleeding was 2% and 0%, respectively, in NEXAVAR-treated patients, and 1.3% and 0.2%, respectively, in placebo-treated patients. There was one fatal hemorrhage in each treatment group in RCC Study 1. If any bleeding necessitates medical intervention, permanent discontinuation of NEXAVAR should be considered.

5.3 Risk of Hypertension

Monitor blood pressure weekly during the first 6 weeks of NEXAVAR. Thereafter, monitor blood pressure and treat hypertension, if required, in accordance with standard medical practice. In the HCC study, hypertension was reported in approximately 9.4% of NEXAVAR-treated patients and 4.3% of patients in the placebo-treated group. In RCC Study 1, hypertension was reported in approximately 16.9% of NEXAVAR-treated patients and 1.8% of patients in the placebo-treated group. Hypertension was usually mild to moderate, occurred early in the course of treatment, and was managed with standard antihypertensive therapy. In cases of severe or persistent hypertension despite institution of antihypertensive therapy, consider temporary or permanent discontinuation of NEXAVAR. Permanent discontinuation due to hypertension occurred in 1 of 297 NEXAVAR-treated patients in the HCC study and 1 of 451 NEXAVAR-treated patients in RCC Study 1.

5.4 Risk of Dermatologic Toxicities

Hand-foot skin reaction and rash represent the most common adverse reactions attributed to NEXAVAR. 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 4 of 297 NEXAVAR-treated patients with HCC and 3 of 451 NEXAVAR-treated patients with RCC.

There have been reports of severe dermatologic toxicities, including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN). These cases may be life-threatening. Discontinue NEXAVAR if SJS or TEN are suspected.

5.5 Risk of Gastrointestinal Perforation

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

5.6 Warfarin

Infrequent bleeding or elevations in the International Normalized Ratio (INR) have been reported in some patients taking warfarin while on NEXAVAR. Monitor patients taking concomitant warfarin regularly for changes in prothrombin time (PT), INR or clinical bleeding episodes.

5.7 Wound Healing Complications

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

5.8 Increased Mortality Observed with NEXAVAR Administered in Combination with Carboplatin/Paclitaxel and Gemcitabine/Cisplatin in Squamous Cell Lung Cancer

In a subset analysis of two randomized controlled trials in chemo-naive patients with Stage IIIB-IV non-small cell lung cancer, patients with squamous cell carcinoma experienced higher mortality with the addition of sorafenib compared to those treated with carboplatin/paclitaxel alone (HR 1.81, 95% CI 1.19–2.74) and gemcitabine/cisplatin alone (HR 1.22, 95% CI 0.82-1.80). The use of sorafenib in combination with carboplatin/paclitaxel is contraindicated in patients with squamous cell lung cancer. Sorafenib in combination with gemcitabine/cisplatin is not recommended in patients with squamous cell lung cancer. The safety and effectiveness of NEXAVAR has not been established in patients with non-small cell lung cancer.

5.9 Risk of QT Interval Prolongation

NEXAVAR can prolong the QT/QTc interval. QT/QTc interval prolongation increases the risk for ventricular arrhythmias. Avoid NEXAVAR in patients with congenital long QT syndrome. Monitor patients with congestive heart failure, bradyarrhythmias, drugs known to prolong the QT interval, including Class Ia and III antiarrhythmics, and electrolyte abnormalities with on-treatment electrocardiograms and electrolytes (magnesium, potassium, calcium) *[see Clinical Pharmacology (12.2)]*.

5.10 Drug-Induced Hepatitis

Sorafenib-induced hepatitis is characterized by a hepatocellular pattern of liver damage with significant increases of transaminases which may result in hepatic failure and death. Increases in bilirubin and INR may also occur. Monitor liver function tests regularly. In case of significantly increased transaminases without alternative explanation such as viral hepatitis or progressing underlying malignancy, discontinue NEXAVAR.

5.11 Risk of Fetal Harm

There are no adequate and well-controlled studies in pregnant women using NEXAVAR. However, based on its mechanism of action and findings in animals, NEXAVAR may cause fetal harm when administered to a pregnant woman. Sorafenib caused embryo-fetal toxicities in animals at maternal exposures that were significantly lower than the human exposures at the recommended dose of 400 mg twice daily. Advise women of childbearing potential to avoid becoming pregnant while on NEXAVAR because of the potential hazard to the fetus *[see Use in Specific Populations (8.1)]*.

6 ADVERSE REACTIONS

The following serious adverse reactions are discussed elsewhere in the labeling:

- Cardiac ischemia, infarction *[see Warnings and Precautions (5.1)]*
- Hemorrhage *[see Warnings and Precautions (5.2)]*
- Hypertension *[see Warnings and Precautions (5.3)]*
- Hand-foot skin reaction, rash, Stevens-Johnson syndrome, and toxic epidermal necrolysis *[see Warnings and Precautions (5.4)]*
- Gastrointestinal perforation *[see Warnings and Precautions (5.5)]*

- QT Interval Prolongation *[see Warnings and Precautions (5.9) and Clinical Pharmacology (12.2)]*
- Drug-Induced Hepatitis *[see Warnings and Precautions (5.10)]*

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The data described in sections 6.1 and 6.2 reflect exposure to NEXAVAR in 748 patients who participated in placebo controlled studies in hepatocellular carcinoma (N=297) or advanced renal cell carcinoma (N=451).

The most common adverse reactions (≥20%), which were considered to be related to NEXAVAR, in patients with HCC or RCC are fatigue, weight loss, rash/desquamation, hand-foot skin reaction, alopecia, diarrhea, anorexia, nausea and abdominal pain.

6.1 Adverse Reactions in HCC Study

Table 2 shows the percentage of patients with HCC experiencing adverse reactions that were reported in at least 10% of patients and at a higher rate in the NEXAVAR arm than the placebo arm. CTCAE Grade 3 adverse reactions were reported in 39% of patients receiving NEXAVAR compared to 24% of patients receiving placebo. CTCAE Grade 4 adverse reactions were reported in 6% of patients receiving NEXAVAR compared to 8% of patients receiving placebo.

Table 2: Adverse Reactions Reported in at Least 10% of Patients and at a Higher Rate in NEXAVAR Arm than the Placebo Arm – HCC Study

	NEXAVAR N=297			**Placebo N=302**		
Adverse Reaction NCI- CTCAE v3 Category/Term	All Grades %	Grade 3 %	Grade 4 %	All Grades %	Grade 3 %	Grade 4 %
Any Adverse Reaction	98	39	6	96	24	8
Constitutional symptoms						
Fatigue	46	9	1	45	12	2
Weight loss	30	2	0	10	1	0
Dermatology/skin						
Rash/desquamation	19	1	0	14	0	0
Pruritus	14	<1	0	11	<1	0
Hand-foot skin reaction	21	8	0	3	<1	0
Dry skin	10	0	0	6	0	0
Alopecia	14	0	0	2	0	0
Gastrointestinal						
Diarrhea	55	10	<1	25	2	0
Anorexia	29	3	0	18	3	<1
Nausea	24	1	0	20	3	0
Vomiting	15	2	0	11	2	0
Constipation	14	0	0	10	0	0
Hepatobiliary/pancreas						
Liver dysfunction	11	2	1	8	2	1
Pain						
Pain, abdomen	31	9	0	26	5	1

Hypertension was reported in 9% of patients treated with NEXAVAR and 4% of those treated with placebo. CTCAE Grade 3 hypertension was reported in 4% of NEXAVAR-treated patients and 1% of placebo-treated patients. No patients were reported with CTCAE Grade 4 reactions in either treatment group.

Hemorrhage/bleeding was reported in 18% of those receiving NEXAVAR and 20% of placebo-treated patients. The rates of CTCAE Grade 3 and 4 bleeding were also higher in the placebo-treated group (CTCAE Grade 3 – 3% NEXAVAR and 5% placebo and CTCAE Grade 4 – 2% NEXAVAR and 4% placebo). Bleeding from esophageal varices was reported in 2.4% in NEXAVAR-treated patients and 4% of placebo-treated patients.

Renal failure was reported in <1% of patients treated with NEXAVAR and 3% of placebo-treated patients.

The rate of adverse reactions (including those associated with progressive disease) resulting in permanent discontinuation was similar in both the NEXAVAR and placebo-treated groups (32% of NEXAVAR-treated patients and 35% of placebo-treated patients).

Laboratory Abnormalities

The following laboratory abnormalities were observed in patients with HCC:

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

Elevated lipase was observed in 40% of patients treated with NEXAVAR compared to 37% of patients in the placebo-treated 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-treated 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).

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-treated patients; no CTCAE Grade 3 or 4 hypoalbuminemia was observed in either group.

INR elevations were observed in 42% of NEXAVAR-treated patients and 34% of placebo-treated patients; CTCAE Grade 3 INR elevations were reported in 4% of NEXAVAR-treated patients and 2% of placebo-treated 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-treated patients.

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

Hypocalcemia was reported in 27% of NEXAVAR-treated patients and 15% of placebo-treated patients. CTCAE Grade 3 hypocalcemia (6–7 mg /dL) occurred in 2% of NEXAVAR-treated patients and 1% of placebo-treated patients. CTCAE Grade 4 hypocalcemia (<6 mg/dL) occurred in 0.4% of NEXAVAR-treated patients and in no placebo-treated patients.

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

6.2 Adverse Reactions in RCC Study 1

Table 3 shows the percentage of patients with RCC experiencing adverse reactions that were reported in at least 10% of patients and at a higher rate in the NEXAVAR arm than the placebo arm. CTCAE Grade 3 adverse reactions were reported in 31% of patients receiving NEXAVAR compared to 22% of patients receiving placebo. CTCAE Grade 4 adverse reactions were reported in 7% of patients receiving NEXAVAR compared to 6% of patients receiving placebo.

Table 3: Adverse Reactions Reported in at Least 10% of Patients and at a Higher Rate in NEXAVAR Arm than the Placebo Arm – RCC Study 1

	NEXAVAR N=451			**Placebo N=451**		
Adverse Reactions NCI- CTCAE v3 Category/Term	All Grades %	Grade 3 %	Grade 4 %	All Grades %	Grade 3 %	Grade 4 %
Any Adverse Reactions	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

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

Laboratory Abnormalities

The following laboratory abnormalities were observed in patients with RCC in Study 1:

Hypophosphatemia was a common laboratory finding, observed in 45% of NEXAVAR-treated patients compared to 11% of placebo-treated patients. CTCAE Grade 3 hypophosphatemia (1–2 mg/dL) occurred in 13% of NEXAVAR-treated patients and 3% of patients in the placebo-treated group. There were no cases of CTCAE Grade 4 hypophosphatemia (<1 mg/dL) reported in either NEXAVAR or placebo-treated 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-treated group. CTCAE Grade 3 or 4 lipase elevations occurred in 12% of patients in the NEXAVAR-treated group compared to 7% of patients in the placebo-treated group. Elevated amylase was observed in 30% of patients treated with NEXAVAR compared to 23% of patients in the placebo-treated group. CTCAE Grade 3 or 4 amylase elevations were reported in 1% of patients in the NEXAVAR-treated group compared to 3% of patients in the placebo-treated 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-treated group.

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

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

Thrombocytopenia was observed in 12% of NEXAVAR-treated patients and 5% of placebo-treated patients. CTCAE Grade 3 or 4 thrombocytopenia was reported in 1% of NEXAVAR-treated patients and in no placebo-treated patients.

Hypocalcemia was reported in 12% of NEXAVAR-treated patients and 8% of placebo-treated patients. CTCAE Grade 3 hypocalcemia (6–7 mg/dL) occurred in 1% of NEXAVAR-treated patients and 0.2% of placebo-treated patients, and CTCAE Grade 4 hypocalcemia (<6 mg/dL) occurred in 1% of NEXAVAR-treated patients and 0.5% of placebo-treated patients.

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

6.3 Additional Data from Multiple Clinical Trials

The following additional drug-related adverse reactions and laboratory abnormalities were reported from clinical trials of NEXAVAR (*very common* 10% or greater, *common* 1 to less than 10%, *uncommon* 0.1% to less than 1%):

Cardiovascular: *Common*: congestive heart failure*[†], myocardial ischemia and/or infarction *Uncommon:* hypertensive crisis* *Rare:* QT prolongation*

Dermatologic: *Very common:* erythema *Common:* exfoliative dermatitis, acne, flushing *Uncommon:* folliculitis, eczema, erythema multiforme, keratoacanthomas/squamous cell cancer of the skin

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

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:* hemorrhage (including gastrointestinal* & respiratory tract* and uncommon cases of cerebral hemorrhage*), asthenia, pain (including mouth, bone, and tumor 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, hypocalcemia, hypokalemia *Uncommon:* dehydration, hyponatremia, transient increases in alkaline phosphatase, increased bilirubin (including jaundice), hypothyroidism, hyperthyroidism

Musculoskeletal: *Common:* arthralgia, myalgia

Nervous System and Psychiatric: *Common:* depression *Uncommon:* tinnitus, reversible posterior leukoencephalopathy*

Renal and Genitourinary: *Common*: renal failure, proteinuria *Rare:* Nephrotic syndrome

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

Respiratory: *Common:* hoarseness *Uncommon:* rhinorrhea, interstitial lung disease-like events (includes reports of pneumonitis, radiation pneumonitis, acute respiratory distress, interstitial pneumonia, pulmonitis and lung inflammation)

In addition, the following medically significant adverse reactions were uncommon during clinical trials of NEXAVAR: transient ischemic attack, arrhythmia, thromboembolism. For these adverse reactions, the causal relationship to NEXAVAR has not been established.

*adverse reactions may have a life-threatening or fatal outcome.

[†]reported in 1.9% of patients treated with sorafenib (N= 2276).

6.4 Postmarketing Experience

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

Dermatologic: Stevens-Johnson syndrome and toxic epidermal necrolysis (TEN)

Hepatobiliary disorders: Drug-induced hepatitis, including reports of hepatic failure and death

Hypersensitivity: Angioedema, anaphylactic reaction

Musculoskeletal: Rhabdomyolysis, osteonecrosis of the jaw

Respiratory: Interstitial lung disease-like events (which may have a life-threatening or fatal outcome)

7 DRUG INTERACTIONS

7.1 Drug Metabolism

Effect of Cytochrome P450 Inducers on Sorafenib

Rifampin, a strong CYP3A4 inducer, administered at a dose of 600 mg once daily for 5 days with a single oral dose of NEXAVAR 400 mg in healthy volunteers resulted in a 37% decrease in the mean AUC of sorafenib. Other inducers of CYP3A4 activity (such as, carbamazepine, dexamethasone, phenobarbital, phenytoin, rifabutin, rifampin, St. John's wort) can increase the metabolism of sorafenib and thus, decrease systemic exposure of sorafenib *[see Dosage and Administration (2) and Clinical Pharmacology (12.3)]*.

Effect of Cytochrome P450 Inhibitors on Sorafenib

Ketoconazole, a strong inhibitor of CYP3A4 and P-glycoprotein, administered at a dose of 400 mg once daily for 7 days did not alter the mean AUC of a single oral dose of NEXAVAR 50 mg in healthy volunteers.

Effect of Sorafenib on Other Drugs

NEXAVAR 400 mg twice daily for 28 days did not increase the systemic exposure of concomitantly administered midazolam (CYP3A4 substrate), dextromethorphan (CYP2D6 substrate), and omeprazole (CYP2C19 substrate). *[see Clinical Pharmacology (12.3)]*.

7.2 Neomycin

Neomycin administered as an oral dose of 1 g three times daily for 5 days decreased the mean AUC of sorafenib by 54% in healthy volunteers administered a single oral dose of NEXAVAR 400 mg. The effects of other antibiotics on the pharmacokinetics of sorafenib have not been studied *[see Clinical Pharmacology (12.3)]*.

7.3 Drugs that Increase Gastric pH

The aqueous solubility of sorafenib is pH dependent, with higher pH resulting in lower solubility. However, omeprazole, a proton pump inhibitor, administered at a dose of 40 mg once daily for 5 days, did not result in a clinically meaningful change in sorafenib single dose exposure. No dose adjustment for NEXAVAR is necessary.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category D *[see Warnings and Precautions (5.11)]*.

Based on its mechanism of action and findings in animals, NEXAVAR may cause fetal harm when administered to a pregnant woman. Sorafenib caused embryo-fetal toxicities in animals at maternal exposures that were significantly lower than the human exposures at the recommended dose of 400 mg twice daily. There are no adequate and well-controlled studies in pregnant women using NEXAVAR. Inform patients of childbearing potential that NEXAVAR can cause birth defects or fetal loss. Instruct both men and women of childbearing potential to use effective birth control during treatment with NEXAVAR and for at least 2 weeks after stopping treatment. Counsel female patients to contact their healthcare provider if they become pregnant while taking NEXAVAR.

When administered to rats and rabbits during the period of organogenesis, sorafenib was teratogenic and induced 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 ≥0.2 mg/kg/day (1.2 mg/m^2/day) in rats and 0.3 mg/kg/day (3.6 mg/m^2/day) in rabbits. These doses result in

exposures (AUC) approximately 0.008 times the AUC seen in 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.

8.3 Nursing Mothers

It is not known whether sorafenib is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from NEXAVAR, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Following administration of radiolabeled 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.

8.4 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.

8.5 Geriatric Use

In total, 59% of HCC patients treated with NEXAVAR were age 65 years or older, and 19% were 75 and older. 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.

8.6 Patients with Hepatic Impairment

In a trial of HCC patients with mild (Child-Pugh A) or moderate (Child-Pugh B) hepatic impairment, the systemic exposure (AUC) of sorafenib was within the range observed in patients without hepatic impairment. In another trial in subjects without HCC, the mean AUC was similar for subjects with mild (n=15) and moderate (n=14) hepatic impairment compared to subjects (n=15) with normal hepatic function. No dose adjustment is necessary for patients with mild or moderate hepatic impairment. The pharmacokinetics of sorafenib have not been studied in patients with severe (Child-Pugh C) hepatic impairment *[see Clinical Pharmacology (12.3)]*.

8.7 Patients with Renal Impairment

No correlation between sorafenib exposure and renal function was observed following administration of a single oral dose of NEXAVAR 400 mg to subjects with normal renal function and subjects with mild (CrCl 50–80 mL/min), moderate (CrCl 30–<50 mL/min), or severe (CrCl <30 mL/min) renal impairment who are not on dialysis. No dose adjustment is necessary for patients with mild, moderate or severe renal impairment who are not on dialysis. The pharmacokinetics of sorafenib have not been studied in patients who are on dialysis *[see Clinical Pharmacology (12.3)]*.

10 OVERDOSAGE

There is no specific treatment for NEXAVAR overdose.

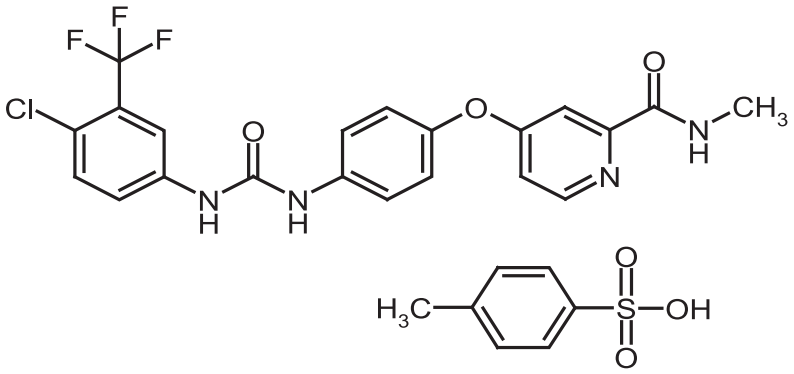
The highest dose of NEXAVAR studied clinically is 800 mg twice daily. The adverse reactions observed at this dose were primarily diarrhea and dermatologic. No information is available on symptoms of acute overdose in animals because of the saturation of absorption in oral acute toxicity studies conducted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

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

11 DESCRIPTION

NEXAVAR, a kinase inhibitor, is the tosylate salt of sorafenib.

Sorafenib tosylate has the chemical name 4-(4-{3-[4-Chloro-3-(trifluoromethyl)phenyl]ureido}phenoxy)N2-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.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Sorafenib is a kinase inhibitor that decreases tumor cell proliferation *in vitro*. Sorafenib was shown to inhibit multiple intracellular (CRAF, BRAF and mutant BRAF) and cell surface kinases (KIT, FLT-3, RET, VEGFR-1, VEGFR-2, VEGFR-3, and PDGFR-ß). Several of these kinases are thought to be involved in tumor cell signaling, angiogenesis, and apoptosis. Sorafenib inhibited tumor growth and angiogenesis of human hepatocellular carcinoma and renal cell carcinoma, and several other human tumor xenografts in immunocompromised mice.

12.2 Pharmacodynamics

Cardiac Electrophysiology

The effect of NEXAVAR 400 mg twice daily on the QTc interval was evaluated in a multi-center, open-label, non-randomized trial in 53 patients with advanced cancer. No large changes in the mean QTc intervals (that is, >20 ms) from baseline were detected in the trial. After one 28-day treatment cycle, the largest mean QTc interval change of 8.5 ms (upper bound of two-sided 90% confidence interval, 13.3 ms) was observed at 6 hours post-dose on day 1 of cycle 2 *[see Warnings and Precautions (5.9)]*.

12.3 Pharmacokinetics

After administration of NEXAVAR tablets, the mean relative bioavailability was 38–49% when compared to an oral solution. The mean elimination half-life of sorafenib was approximately 25 to 48 hours. Multiple doses of NEXAVAR for 7 days resulted in a 2.5- to 7-fold accumulation compared to a single dose. Steady-state plasma sorafenib concentrations were achieved within 7 days, with a peak-to-trough ratio of mean concentrations of less than 2.

Absorption and Distribution: Following oral administration, sorafenib reached peak plasma levels in approximately 3 hours. With a moderate-fat meal (30% fat; 700 calories), bioavailability was similar to that in the fasted state. With a high-fat meal (50% fat; 900 calories), bioavailability was reduced by 29% compared to that in the fasted state. It is recommended that NEXAVAR be administered without food *[see Dosage and Administration (2)]*.

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

Metabolism and Elimination: Sorafenib undergoes oxidative metabolism by hepatic CYP3A4, as well as glucuronidation by UGT1A9. Inducers of CYP3A4 activity can decrease the systemic exposure of sorafenib *[see Dosage and Administration (2) and Drug Interactions (7.1)]*.

Sorafenib accounted for approximately 70–85% of the circulating analytes in plasma at steady-state. Eight metabolites of sorafenib have been identified, of which 5 have been detected in plasma. The main circulating metabolite of sorafenib, the pyridine N-oxide that comprises approximately 9–16% of circulating analytes at steady-state, showed *in vitro* potency similar to that of sorafenib.

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.

Effects of Age, Gender and Race: A study of the pharmacokinetics of sorafenib indicated that the mean AUC of sorafenib in Asians (N=78) was 30% lower than in Caucasians (N=40). Gender and age do not have a clinically meaningful effect on the pharmacokinetics of sorafenib.

Renal Impairment: Mild (CrCl 50-80 mL/min), moderate (CrCl 30 - <50 mL/min), and severe (CrCl <30 mL/min) renal impairment do not affect the pharmacokinetics of sorafenib. No dose adjustment is necessary *[see Use in Specific Populations (8.7)]*.

Hepatic Impairment: Mild (Child-Pugh A) and moderate (Child-Pugh B) hepatic impairment do not affect the pharmacokinetics of sorafenib. No dose adjustment is necessary *[see Use in Specific Populations (8.6)]*.

Drug-Drug Interactions: Studies in human liver microsomes demonstrated that sorafenib competitively inhibited CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A4. However, NEXAVAR 400 mg twice daily for 28 days with substrates of CYP3A4, CYP2D6 and CYP2C19 did not increase the systemic exposure of these substrates *[see Drug Interactions (7.1)]*.

Studies with cultured human hepatocytes demonstrated that sorafenib did not increase CYP1A2 and CYP3A4 activities, suggesting that sorafenib is unlikely to induce CYP1A2 or CYP3A4 in humans.

Sorafenib inhibits glucuronidation by UGT1A1 and UGT1A9 *in vitro*. NEXAVAR could increase the systemic exposure of concomitantly administered drugs that are UGT1A1 or UGT1A9 substrates.

Sorafenib inhibited P-glycoprotein *in vitro*. NEXAVAR could increase the concentrations of concomitantly administered drugs that are P-glycoprotein substrates.

13 NONCLINICAL TOXICOLOGY

13.1 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 function 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 ≥ 5 mg/kg (30 mg/m^2). This dose results in an exposure (AUC) that is approximately 0.5 times the AUC in patients at the recommended human dose. Dogs showed tubular degeneration in the testes at 30 mg/kg/day (600 mg/m^2/day). This dose results in an exposure that is approximately 0.3 times the AUC at the recommended human dose. Oligospermia was observed in dogs at 60 mg/kg/day (1200 mg/m^2/day) of sorafenib.

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

14 CLINICAL STUDIES

The clinical safety and efficacy of NEXAVAR have been studied in patients with hepatocellular carcinoma (HCC) and renal cell carcinoma (RCC).

14.1 Hepatocellular Carcinoma

The **HCC Study** was a Phase 3, international, multicenter, randomized, double blind, placebo-controlled trial in patients with unresectable hepatocellular carcinoma. Overall survival was the primary endpoint. A total of 602 patients were randomized; 299 to NEXAVAR 400 mg twice daily and 303 to matching placebo.

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

The trial was stopped for efficacy following a pre-specified second interim analysis for survival showing a statistically significant advantage for NEXAVAR over placebo for overall survival (HR: 0.69, p= 0.00058) (see Table 4 and Figure 1). This advantage was consistent across all subsets analyzed.

Final analysis of time to tumor progression (TTP) based on data from an earlier time point (by independent radiologic review) also was significantly longer in the NEXAVAR arm (HR: 0.58, p=0.000007) (see Table 4).

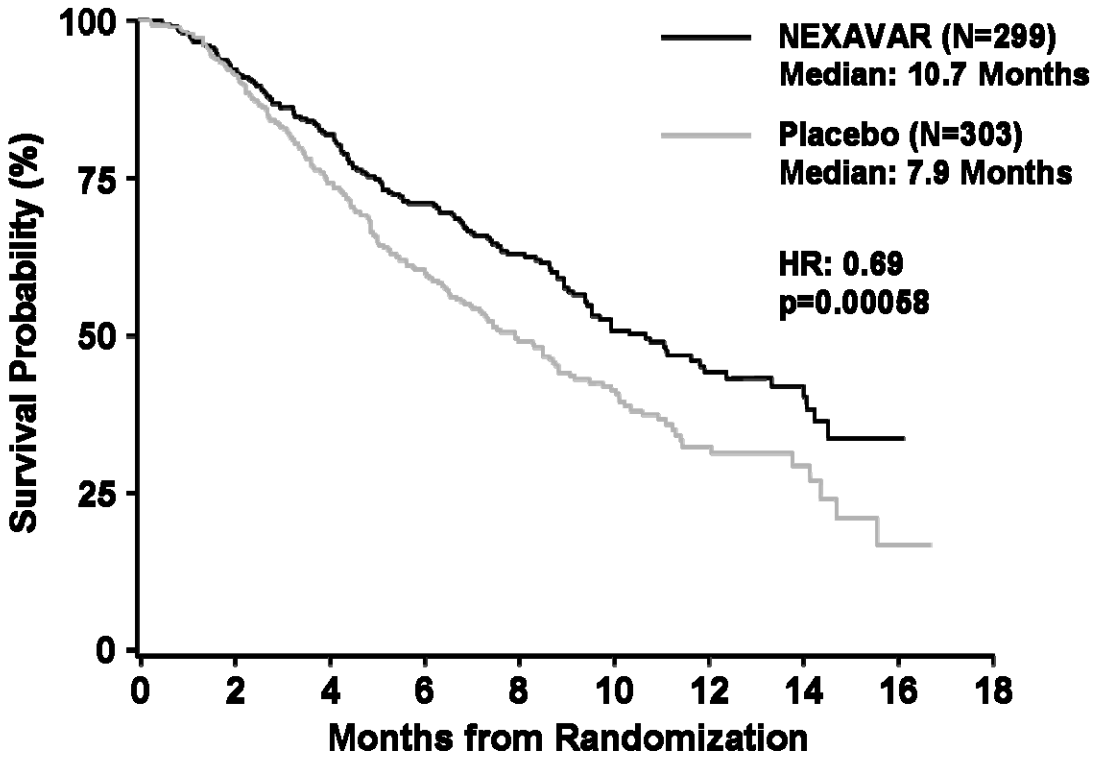
Table 4: Efficacy Results from HCC Study

Efficacy Parameter	**NEXAVAR (N=299)**	**Placebo (N=303)**	**Hazard Ratio[1] (95% CI)**	**P-value (log-rank test[2])**
Overall Survival **Median, months** **(95% CI)** **No. of events**	 10.7 (9.4, 13.3) 143	 7.9 (6.8, 9.1) 178	 0.69 (0.55, 0.87)	0.00058
Time to Progression [3] **Median, months** **(95% CI)** **No. of events**	 5.5 (4.1, 6.9) 107	 2.8 (2.7, 3.9) 156	 0.58 (0.45, 0.74)	0.000007

CI=Confidence interval

1. Hazard ratio, sorafenib/placebo, stratified Cox model
2. Stratified log rank (for the interim analysis of survival, the stopping boundary one-sided alpha = 0.0077)
3. The time-to-progression (TTP) analysis, based on independent radiologic review, was based on data from an earlier time point than the survival analysis

Figure 1: Kaplan-Meier Curve of Overall Survival in HCC Study (Intent-to-Treat Population)



Patients at Risk									
NEXAVAR	270	234	200	140	89	48	24	1	0
Placebo	272	217	174	108	69	31	14	3	0

14.2 Renal Cell Carcinoma

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

RCC 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 (low or intermediate) and country and randomized to NEXAVAR 400 mg twice daily (N=384) or to placebo (N=385).

Table 5 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-treated groups, respectively.

Table 5: Demographic and Disease Characteristics – RCC Study 1

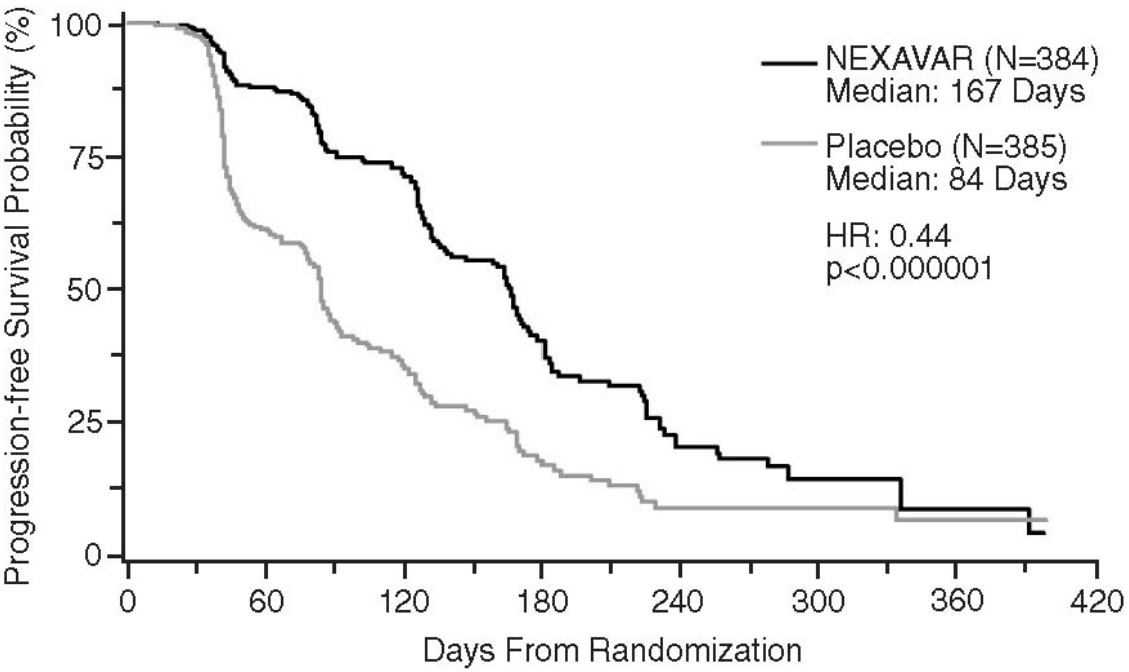
Characteristics	NEXAVAR N=384		Placebo N=385	
	n	**(%)**	**n**	**(%)**
Gender				
Male	267	(70)	287	(75)
Female	116	(30)	98	(25)
Race				
White	276	(72)	278	(73)
Black/Asian/ Hispanic/Other	11	(3)	10	(2)
Not reported [a]	97	(25)	97	(25)
Age group				
< 65 years	255	(67)	280	(73)
≥ 65 years	127	(33)	103	(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				
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 2 depicts Kaplan-Meier curves for PFS. The PFS analysis was based on a two-sided Log-Rank test stratified by MSKCC prognostic risk category and country.

Figure 2: Kaplan-Meier Curves for Progression-free Survival – RCC Study 1



NOTE: HR is from Cox regression model with the following covariates: MSKCC prognostic risk category and country. P-value is from two-sided Log-Rank test stratified by MSKCC prognostic risk category 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, 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 radiologic review according to RECIST criteria. Overall, of 672 patients who were evaluable for response, 7 (2%) NEXAVAR-treated patients and 0 (0%) placebo-treated 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.

RCC 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 RCC 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, 79 patients with RCC 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-treated group (163 days) than in the placebo-treated group (41 days) (p=0.0001, HR=0.29).

16 HOW SUPPLIED/STORAGE AND HANDLING

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 50419-488-58

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.

17 PATIENT COUNSELING INFORMATION

See FDA-approved Patient Labeling

17.1 Cardiac Ischemia; Infarction

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 *[see Warnings and Precautions (5.1)]*.

17.2 Bleeding

Inform patients that NEXAVAR can increase the risk of bleeding and that they should promptly report any episodes of *bleeding [see Warnings and Precautions (5.2)]*.

Inform patients that bleeding or elevations in the International Normalized Ratio (INR) have been reported in some patients taking warfarin while on NEXAVAR and that their INR should be monitored regularly *[see Warnings and Precautions (5.6)]*.

17.3 Hypertension

Inform patients that hypertension can develop during NEXAVAR treatment, especially during the first six weeks of therapy, and that blood pressure should be monitored regularly during treatment *[see Warnings and Precautions (5.3)]*.

17.4 Skin Reactions

Advise patients of the possible occurrence of hand-foot skin reaction and rash during NEXAVAR treatment and appropriate countermeasures *[see Warnings and Precautions (5.4)]*.

17.5 Gastrointestinal Perforation

Advise patients that cases of gastrointestinal perforation have been reported in patients taking NEXAVAR *[see Warnings and Precautions (5.5)]*.

17.6 Wound Healing Complications

Inform patients that temporary interruption of NEXAVAR is recommended in patients undergoing major surgical procedures *[see Warnings and Precautions (5.7)]*.

17.7 QT Interval Prolongation

Inform patients with a history of prolonged QT interval that NEXAVAR can worsen the condition *[see Warnings and Precautions (5.9) and Clinical Pharmacology (12.2)]*.

17.8 Drug-Induced Hepatitis

Inform patients that NEXAVAR can cause hepatitis which may result in hepatic failure and death. Advise patients that liver function tests should be monitored regularly during treatment and to report signs and symptoms of hepatitis *[see Warnings and Precautions (5.10)]*.

17.9 Birth Defects and Fetal Loss

Inform patients that NEXAVAR can cause birth defects or fetal loss. Counsel both male and female patients to use effective birth control during treatment with NEXAVAR and for at least 2 weeks after stopping treatment. Inform female patients to contact their healthcare provider if they become pregnant while taking NEXAVAR *[see Warnings and Precautions (5.11), Use in Specific Populations (8.1)]*.

17.10 Nursing Mothers

Advise mothers not to breast-feed while taking NEXAVAR *[see Use in Specific Populations (8.3)]*.

17.11 Missed Doses

Instruct patients that if a dose of NEXAVAR is missed, to take the next dose at the regularly scheduled time, and not double the dose. Instruct patients to contact their healthcare provider immediately if they take too much NEXAVAR.

Patient Information:
NEXAVAR® (NEX-A-VAR)
(sorafenib)
tablets, oral

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

What is NEXAVAR?

NEXAVAR is an anticancer medicine used to treat a certain type of liver or kidney cancer called:

- Hepatocellular carcinoma (HCC, a type of liver cancer), when it can not be treated with surgery
- Renal cell carcinoma (RCC, a type of kidney cancer)

NEXAVAR has not been studied in children.

Who should not take NEXAVAR?

Do not take NEXAVAR if you:

- are allergic to sorafenib or any of the other ingredients of NEXAVAR. See the end of this leaflet for a complete list of ingredients in NEXAVAR.
- have a specific type of lung cancer (squamous cell) and receive carboplatin and paclitaxel.

What should I tell my doctor before taking NEXAVAR?

Before you take NEXAVAR, tell your doctor if you:

- have any allergies
- have heart problems, including a problem called “congenital long QT syndrome”
- have chest pain
- have bleeding problems
- have high blood pressure
- plan to have any surgical procedures
- have lung cancer or are being treated for lung cancer

- have kidney problems in addition to kidney cancer
- have liver problems in addition to liver cancer
- are pregnant or plan to become pregnant. See **"What are the possible side effects of NEXAVAR?"**
- are breast-feeding or planning to breast-feed. It is not known if NEXAVAR passes into your breast milk. You and your doctor should decide if you will take NEXAVAR or breast-feed. You should not do both.

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 are taking the following medicines:

- **warfarin (Coumadin, Jantoven®)**
- **neomycin**
- **St. Johns Wort**
- **dexamethasone**
- **phenytoin (Fosphenytoin sodium, Dilantin, Phenytek)**
- **carbamazepine (Carbatrol, Equetro, Tegretol. Teril, Epitol)**
- **rifampin (Rifater, Rifamate, Rifadin, Rimactane)**
- **rifabutin (Mycobutin)**
- **phenobarbital**

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

How should I take NEXAVAR?

- Take NEXAVAR exactly as prescribed by your doctor.
- The usual dose of NEXAVAR is 2 tablets taken two times a day (for a total of 4 tablets each day). Your doctor may change your dose during treatment or stop treatment for some time if you have side effects.
- Take NEXAVAR without food (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.
- If you take too much NEXAVAR call your doctor or go to the nearest hospital emergency room right away.

What are the possible side effects of NEXAVAR?

NEXAVAR may cause serious side effects, including:

- **decreased blood flow to the heart and heart attack.** Get emergency help right away and call your doctor if you get symptoms such as chest pain, shortness of breath, feel lightheaded or faint, nausea, vomiting, sweating a lot.

- **bleeding problems.** NEXAVAR can cause bleeding which can be serious and sometimes lead to death. Tell your doctor if you have any bleeding while taking NEXAVAR.
- **high-blood pressure.** Your blood pressure should be checked every week during the first 6 weeks of starting NEXAVAR. Your blood pressure should be checked regularly and any high blood pressure should be treated while you are receiving 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 change your dose or stop treatment for some time.
- **serious skin and mouth reactions.** NEXAVAR can cause serious skin reactions which can be life-threatening. Tell your doctor if you have any of the following symptoms:
  - skin rash
  - blistering and peeling of the skin
  - blistering and peeling on the inside of your mouth
- **an opening in the wall of your stomach or intestines (perforation of the bowel)**. Tell your doctor right away if you get high fever, nausea, vomiting, severe stomach or abdominal pain.
- **possible wound healing problems.** If you need to have a surgical procedure, tell your doctor that you are taking NEXAVAR. NEXAVAR may need to be stopped until your wound heals after some types of surgery.
- **changes in the electrical activity of your heart called QT prolongation.** QT prolongation can cause irregular heartbeats that can be life-threatening. Your doctor may do tests during your treatment with NEXAVAR to check the levels of potassium, magnesium, and calcium in your blood, and check the electrical activity of your heart with an ECG. Tell your doctor right away if you feel faint, lightheaded, dizzy or feel your heart beating irregularly or fast while taking NEXAVAR.
- **inflammation of your liver (drug-induced hepatitis).** NEXAVAR may cause liver problems that may lead to liver failure and death. Your doctor may stop your treatment with NEXAVAR if you develop changes in certain liver function tests. Call your doctor right away if you develop any of the following symptoms:
  - your skin or the white part of your eyes turns yellow (jaundice)
  - dark “tea-colored” urine
  - light-colored bowel movements (stools)
  - worsening nausea
  - worsening vomiting
  - abdominal pain
- **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. Talk with your doctor about effective birth control methods. Call your doctor right away if you become pregnant during treatment with NEXAVAR.

The most common side effects of NEXAVAR include:

- rash, redness, itching or peeling of your skin
- hair thinning or patchy hair loss
- diarrhea (frequent or loose bowel movements)

- nausea or vomiting
- loss of appetite
- abdominal pain
- tiredness
- weight loss

Tell your doctor if you have any side effect that bothers you or that does not go away. These are not all the possible side effects of NEXAVAR. Ask your doctor or pharmacist for more information.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store NEXAVAR?

- Store NEXAVAR tablets at room temperature between 68° F to 77° F (20° C to 25° C).
- Store NEXAVAR tablets 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 give NEXAVAR to other people even if they have the same symptoms you have. It may harm them.

This Patient Information 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.

For more information, go to www.NEXAVAR.com, or call (1-866-639-2827).

What are the ingredients in NEXAVAR?

Active Ingredient: sorafenib tosylate

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

This Patient Information has been approved by the U.S. Food and Drug Administration.

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