蕾莎瓦® 膜衣錠 200毫克
Nexavar® film-coated tablets 200 mg

衛署藥輸字第024727號
本藥須由醫師處方使用

1. 品名
蕾莎瓦® 膜衣錠200毫克

2. 適應症
2.1 轉移性或無法手術切除且不適合局部治療或局部治療失敗之晚期肝細胞癌(HCC)。
說明：本適應症之樞紐性試驗(試驗100554)所納入的試驗族群中，在以Child-Pugh評分，主要為Child-Pugh class A患者，少數為Child-Pugh class B患者[參見臨床研究(14.1)]。
2.2 晚期腎細胞癌(RCC)且已接受interferon-alpha或interleukin-2治療失敗，或不適合以上兩種藥物治療之病患。
2.3 放射性碘治療無效之局部晚期或轉移性的進行性(progressive)分化型甲狀腺癌(DTC)。

3. 劑量與使用方法
Nexavar的每日建議劑量為一次400毫克(2顆200毫克錠劑)，一天服用2次，不與食物一起服用(至少用餐前一小時或用餐後2小時)。口服使用，以水吞服。治療應持續直到病患無法再得到臨床效益或發生不可接受的毒性。

肝細胞癌及腎細胞癌的劑量調整方式

處理疑似藥物不良反應時，可能需要暫時中斷Nexavar治療及/或減少劑量。當必須要減少劑量時，Nexavar的劑量應降至每天400毫克，若須進一步減少劑量，Nexavar的劑量可以降至每隔一天400毫克[參見警語和注意事項(6)]。

因皮膚毒性而劑量調整的建議如下表1所示：

表1：肝細胞或腎細胞癌病患因皮膚毒性的劑量調整建議

皮膚毒性分級	發生	Nexavar劑量調整
第1級：麻木、感覺遲鈍、感覺異常、刺痛、無痛腫大、紅斑或手或腳的不舒服感但不影響病患的日常活動	任何時候	持續Nexavar治療並考慮局部治療以緩解症狀
第2級：疼痛的紅斑及手或腳的腫大及/或會影響病患日常活動的不舒服感	第一次發生	持續Nexavar治療並考慮局部治療以緩解症狀 若七天內沒有改善，如以下方式處理
	若七天內沒有	中斷Nexavar治療，直到毒性改善到第0-1級

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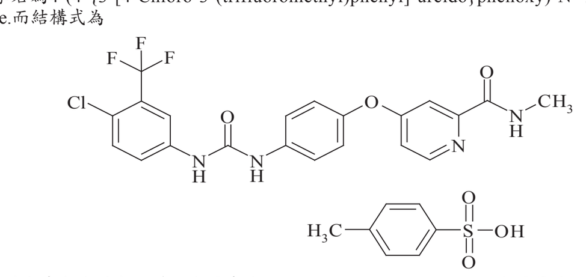


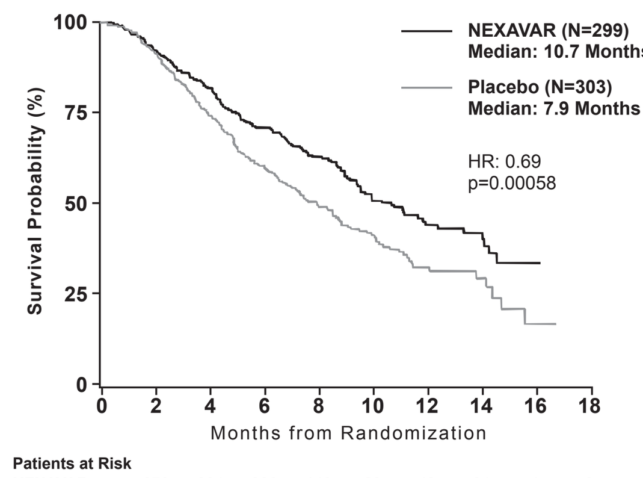
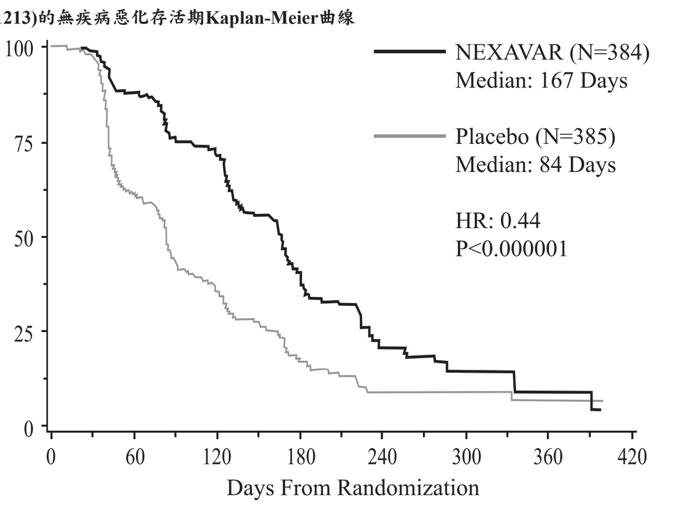


圖2：RCC試驗1 (試驗11213)的無疾病惡化存活期Kaplan-Meier曲線



註：HR是來自涵蓋下列共變數的Cox迴歸分析(Cox regression model)：MSKCC預後風險分級及國家。P值是來自依預後風險及國家分組的雙邊對數系列檢定來分析。

Nexavar組的無疾病惡化存活期中位數是167天，比較安慰劑組是84天。估計危險比例(hazard ratio，Nexavar相對於安慰劑的死亡風險程度)為0.44 (95% CI: 0.35, 0.55)。

無疾病惡化存活期(PFS)以探索性統計方式分析在不同病患群中研究，包括年齡大於或小於65歲、ECOG評估身體狀況等級為0或1、MSKCC預後風險分級、是否曾因轉移性疾病惡化或在疾病早期有做治療、預後時間短於或長於1.5年。在這些分群中Nexavar對無疾病惡化存活期的影響是一致的，包括之前未曾接受IL-2或干擾素治療的病患(n = 137; Nexavar組有65名而安慰劑組有72名)，而其無疾病惡化存活期中位數在Nexavar組為172天而安慰劑組為85天。

腫瘤反應是藉由獨立醫師檢查放射性影像並依腫瘤測量標準(RECIST)來評斷。整體而言可以分析反應的672名病患中，7名Nexavar病患(0.2%)有經確認的局部反應；而無一安慰劑組病患有經確認的局部反應。因此Nexavar治療組病患PFS的延長主要反應在穩定疾病族群。

於220個死亡案例時的期中存活率分析，相較於安慰劑組，Nexavar組在總存活期較長，危險比例(hazard ratio)估計為0.72。此分析結果並未符合預先定義的顯著統計標準，計劃在存活資料齊全時再完成更多的分析。

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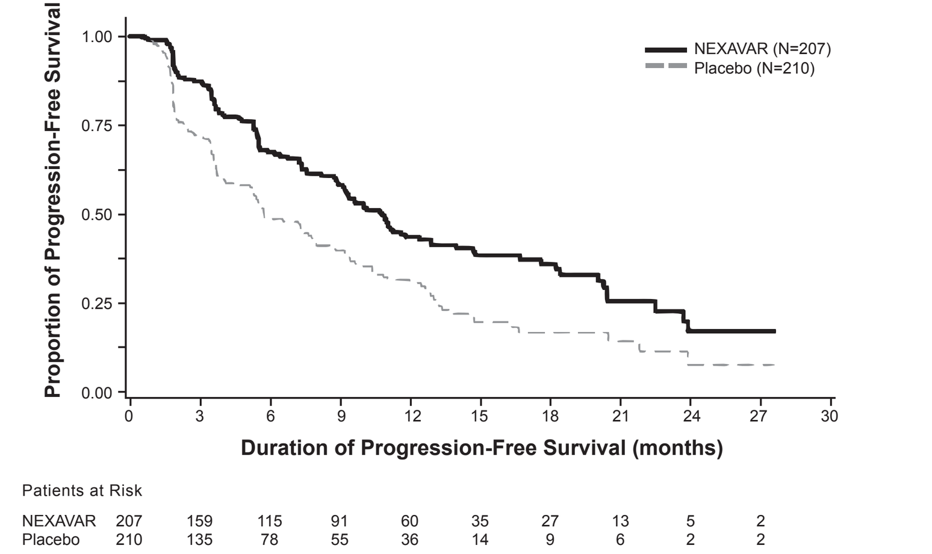


NEXAVAR® film-coated tablets 200mg

1 NAME OF THE MEDICINAL PRODUCT

NEXAVAR® 200 mg film-coated tablets

2 INDICATIONS AND USAGE

2.1 Hepatocellular Carcinoma

NEXAVAR is indicated for the treatment of patients with metastatic or unresectable advanced hepatocellular carcinoma (HCC) and inappropriate to local treatment or local treatment failure.

Statement: In the pivotal study for the HCC indication (study 100554), by Child-Pugh score the majority of enrolled groups are Child-Pugh class A and the minority are Child-Pugh class B patients [*see Clinical Studies (14.1)*].

2.2 Renal Cell Carcinoma

NEXAVAR is indicated for the treatment of patients with advanced renal cell carcinoma (RCC) who have failed prior interferon-alpha or interleukin-2 based therapy or are considered unsuitable for such therapy.

2.3 Differentiated Thyroid Carcinoma

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

3 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). For oral use. To be swallowed with a glass of water. Treatment should continue until the patient is no longer clinically benefiting from therapy or until unacceptable toxicity occurs.

Dose modification for Hepatocellular Carcinoma and Renal Cell Carcinoma

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 Warnings and Precautions (6)]*.

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

Table 1: Suggested Dose Modifications for Dermatologic Toxicities in Patients with hepatocellular or Renal Cell Carcinoma

Dermatologic 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 orperform 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

Dose modifications for Differentiated Thyroid Carcinoima

Management of suspected adverse drug reactions may require temporary interruption and/or dose reduction of NEXAVAR therapy.

When dose reduction is necessary during the treatment of differentiated thyroid carcinoma, the NEXAVAR dose should be reduced to 600mg daily in divided doses (two tablets of 200 mg and one tablet of 200 mg twelve hours apart). If additional dose reduction is necessary, NEXAVAR may be reduced to one tablet of 200 mg twice daily, followed by one tablet of 200 mg once daily. After improvement of non-hematological adverse reactions, the dose of NEXAVAR may be increased.

Table 2: Recommended Doses for Patients with Differentiated Thyroid Carcinoma Requiring Dose Reduction

Dose Reduction	NEXAVAR Dose	
First Dose Reduction	600 mg daily dose	400 mg and 200 mg 12 hours apart (2 tablets and 1 tablet 12 hours apart – either dose can come first)
Second Dose Reduction	400 mg daily dose	200 mg twice daily (1 tablet twice daily)
Third Dose Reduction	200 mg daily dose	200 mg once daily (1 tablet once daily)

When dose reduction is necessary for dermatology toxicities, reduce the NEXAVAR dose as indicated in Tablet 3 below.

Table 3: Recommended Dose Modifications for Dermatologic Toxicities for Patients with Differentiated Thyroid Carcinoma

Dermatologic Toxicity Grade	Occurrence	NEXAVAR 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
Grade 2: Painful erythema and swelling of the hands or feet and/or discomfort affecting the patient's normal activities	1st occurrence	Decrease NEXAVAR dose to 600 mg daily If no improvement within 7 days, see below
	No improvement within 7 days at reduced dose or 2nd Occurrence	Interrupt NEXAVAR until resolved or improved to grade 1 If NEXAVAR is resumed, decrease dose (see Table 2)
	3rd occurrence	Interrupt NEXAVAR until resolved or improved to grade 1 If NEXAVAR is resumed, decrease dose (see Table 2)
	4th occurrence	Discontinue NEXAVAR permanently
Grade 3: Moist desquamation, ulceration, blistering, or severe pain of the hands or feet, resulting in inability to work or perform activities of daily living	1st occurrence	Interrupt NEXAVAR until resolved or improved to grade 1 If NEXAVAR is resumed, decrease dose by one dose level (see Table 2)
	2nd occurrence	Interrupt NEXAVAR until resolved or improved to grade 1 When NEXAVAR is resumed, decrease dose by two dose levels (see Table 2)
	3rd occurrence	Discontinue NEXAVAR permanently

Following improvement of Grade 2 or 3 dermatologic toxicity to Grade 0–1 after at least 28 days of treatment on a reduced dose of NEXAVAR, the dose of NEXAVAR may be increased one dose level from the reduced dose. Approximately 50% of patients requiring a dose reduction for dermatologic toxicity are expected to meet these criteria for resumption of the higher dose and roughly 50% of patients resuming the previous dose are expected to tolerate the higher dose (that is, maintain the higher dose level without recurrent Grade 2 or higher dermatologic toxicity).

No dose adjustment is required on the basis of patient age, gender, or body weight.

Concomitant Strong CYP3A4 inducers: The use of concomitant strong CYP3A4 inducers may decrease sorafenib plasma concentrations and should be avoided (eg, St. John's Wort, dexamethasone, phenytoin, carbamazepine, rifampin, rifabutin, phenobarbital). Although a dose increase has not been studied, if a strong CYP3A4 inducer must be co-administered, a NEXAVAR dose increase may be considered. If the dose of NEXAVAR is increased, the patient should be monitored carefully for toxicity *[see DRUG INTERACTIONS (8.7)]*.

4 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 for oral use with a diameter of 10 mm and a weight of 350 mg, debossed with the "Bayer cross" on one side and "200" on the other side.

5 CONTRAINDICATIONS

- NEXAVAR is contraindicated in patients with known severe hypersensitivity to sorafenib or any other component of NEXAVAR.
- NEXARVAR in combination with carboplatin and paclitaxel is contraindicated in patients with squamous cell lung cancer *[see 6 warning and precaution (6.12)]*.

6 WARNINGS AND PRECAUTIONS

6.1 Risk of Cardiac Ischemia and/or Infarction

In the HCC study, the incidence of cardiac ischemia/infarction was 2.7% in NEXAVAR patients compared with 1.3% in the placebo-treated group, 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%), and in the DTC study, the incidence of cardiac ischemia/infarction was 1.9% in the NEXAVAR-treated group compared with 0% in the placebo-treated group. 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.

6.2 QT interval prolongation

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

6.3 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. In the DTC study, bleeding was reported in 17.4% of NEXAVAR-treated patients and 9.6% of placebo-treated patients; however the incidence of CTCAE Grade 3 bleeding was 1% in NEXAVAR-treated patients and 1.4% in placebo-treated patients. There was no Grade 4 bleeding reported and there was one fatal hemorrhage in a placebo-treated patient. If any bleeding necessitates medical intervention, permanent discontinuation of NEXAVAR should be considered. Due to the potential risk of bleeding, tracheal, bronchial, and esophageal infiltration should be treated with local therapy prior to administering NEXAVAR in patients with DTC.

6.4 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 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. In the DTC study, hypertension was reported in 40.6% of NEXAVAR-treated patients and 12.4% of placebo-treated patients. 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, and 1 of 207 NEXAVAR-treated patients in the DTC study.

6.5 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 CTC (National Cancer Institute Common Toxicity Criteria) 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, and 11 (5.3%) of 207 NEXAVAR-treated patients with DTC.

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

6.6 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.

6.7 Warfarin

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

6.8 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.

6.9 Interaction with Neomycin

Co-administration of neomycin may cause a decrease in sorafenib bioavailability *[see Drug-Drug Interactions (8.5)]*.

6.10 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 (9.1)]*.

6.11 Hepatic Impairment

Hepatic impairment may reduce plasma concentrations of sorafenib. Comparison of data across studies

suggests that sorafenib levels are lower in HCC patients than in non-HCC patients (without hepatic impairment). The AUC of sorafenib is similar between HCC patients with mild (Child-Pugh A) and moderate (Child-Pugh B) hepatic impairment. The optimal dose in non-HCC patients with hepatic impairment is not established *[see Use in Specific Populations (9.7) and Clinical Pharmacology (12.2)]*

6.12 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 NEXAVAR 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 NEXAVAR in combination with carboplatin/paclitaxel is contraindicated in patients with squamous cell lung cancer. NEXAVAR 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 [see Undesirable effects (7.5)].

6.13 Hypocalcaemia

When using NEXAVAR in patients with differentiated thyroid carcinoma, close monitoring of blood calcium level is recommended. In clinical trials, hypocalcaemia was more frequent and more severe in patients with differentiated thyroid carcinoma, especially with a history of hypoparathyroidism, compared to patients with renal cell or hepatocellular carcinoma *[see Undesirable effects (7.3)]*.

6.14 Impairment of Thyroid Stimulating Hormone Suppression in Differentiated Thyroid Carcinoma

NEXAVAR impairs exogenous thyroid suppression. In the DTC study, 99% of patients had a baseline thyroid stimulating hormone (TSH) level less than 0.5 mU/L. Elevation of TSH level above 0.5 mU/L was observed in 41% of NEXAVAR-treated patients as compared with 16% of placebo-treated patients. For patients with impaired TSH suppression while receiving NEXAVAR, the median maximal TSH was 1.6 mU/L and 25% had TSH levels greater than 4.4 mU/L.

Monitor TSH levels monthly and adjust thyroid replacement medication as needed in patients with DTC.

6.15 Keratoacanthoma and skin squamous cell carcinoma

When using NEXAVAR, keratoacanthoma and skin squamous cell carcinoma may be occurred. In DTC study, 8 cases of skin squamous cell carcinoma have been reported in NEXAVAR group (7 cases from the double blind period and 1 case from the open label period), compared to control group is zero. Among these 8 patients with skin squamous cell carcinoma, all were recovered after surgical treatment. Clinically it should be examined carefully and receive assessment and appropriate management by dermatologists in case of detecting abnormality.

7 Undesirable effects

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

- Cardiac ischemia, infarction *[See Warnings and Precautions (6.1)]*
- Hemorrhage *[See Warnings and Precautions (6.3)]*
- Hypertension *[See Warnings and Precautions (6.4)]*
- Hand-foot skin reaction, rash, Stevens-Johnson syndrome, and toxic epidermal necrolysis *[See Warnings and Precautions (6.5)]*
- Gastrointestinal perforation *[See Warnings and Precautions (6.6)]*
- QT Interval Prolongation *[see Warnings and Precautions (6.2) and Pharmacodynamics (12.3)]*
- Impairment of TSH suppression in DTC *[see Warnings and Precautions (6.14)]*
- *thromboembolism*

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

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 7.1, 7.2 and 7.3 reflect exposure to NEXAVAR in 955 patients who participated in placebo controlled studies in hepatocellular carcinoma (n=297) or advanced renal cell carcinoma (n=451), or differentiated thyroid carcinoma (N = 207).

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

7.1 Adverse Reactions in HCC Study

Table 4 and 5 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 4 : Adverse Reactions Reported in at Least 10% of Patients and at a Higher Rate in NEXAVAR Arm than the Placebo Arm – HCC Study 1 (Study 100554) *[See Clinical Studies(13)]*

Adverse Event* NCI- CTCAE v3 Category/Term	NEXAVAR N=297 All Grades %	Grade 3 %	Grade 4 %	Placebo N=302 All Grades %	Grade 3 %	Grade 4 %
Any Event	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 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 groups (32% of NEXAVAR patients and 35% of placebo patients).

Table 5 : Adverse reactions reported in at least 10% of patients and at a higher rate in NEXAVAR arm than the Placebo Arm – HCC Study 2 (Study 11849) *[See Clinical Studies(14)]*

NCI-CTCAE v3 System organ class / Preferred term	NEXAVAR (N = 149) All Grades %	Grade 3 %	Grade 4 %	Placebo (N = 75) All Grades %	Grade 3 %	Grade 4 %
Any Adverse Reaction	98	36	9	95	31	7
Blood/Bone Narrow						
Hemoglobin	20	4	4	15	0	0
Leukocytes	11	1	0	8	4	0
Platelets	22	4	2	13	1	0
Cardiac General						
Hypertension	22	3	0	5	1	0
Constitutional Symptoms						
Fatigue	34	5	0	20	4	0
Fever	26	2	0	11	3	0
Weight Loss	42	3	0	17	1	0
Dermatology/Skin						
Alopecia	27	0	0	1	0	0
Hand-foot skin reaction	46	11	0	3	0	0
Pruritus	12	0	0	12	1	0
Rash/Desquamation	22	1	0	9	0	0
Gastrointestinal						
Anorexia	31	3	0	17	3	0
Ascites	26	7	0	17	9	0
Diarrhea	42	7	0	16	0	0
Metabolic/Laboratory						
Alkaline phosphatase	26	4	0	19	1	0
ALT	32	5	1	24	7	0
AST	41	18	1	31	15	4
Bilirubin	36	12	5	32	7	11
Hypoalbuminemia	22	0	0	21	0	0
Hyponatremia	15	8	1	13	8	0
Hypophosphatemia	11	3	0	5	1	0
Lipase	13	2	0	5	0	0
Pain						
Pain, abdomen nos	35	7	0	20	4	0
Pain, back	15	3	0	12	1	0
Pulmonary/Upper respiratory						
Cough	18	1	0	15	0	0

Laboratory abnormalities in HCC patients (study 100554)

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

Elevated lipase was observed in 40% of patients treated with NEXAVAR compared to 37% of patients in the placebo group. CTCAE Grade 3 or 4 lipase elevations occurred in 9% of patients in each group. Elevated amylase was observed in 34% of patients treated with NEXAVAR compared to 29% of patients in the placebo group. CTCAE Grade 3 or 4 amylase elevations were reported in 2% of patients in each group. Many of the lipase and amylase elevations were transient, and in the majority of cases, NEXAVAR treatment was not interrupted. Clinical pancreatitis was reported in 1 of 297 NEXAVAR-treated patients (CTCAE Grade 2).

Elevations in liver function tests were comparable between the 2 arms of the study. Hypoalbuminemia was observed in 59% of NEXAVAR-treated patients and 47% of placebo patients; no CTCAE Grade 3 or 4 hypoalbuminemia was observed in either group.

INR elevations were observed in 42% of NEXAVAR-treated patients and 34% of placebo patients; CTCAE Grade 3 INR elevations were reported in 4% of NEXAVAR-treated patients and 2% of placebo patients; there was no CTCAE Grade 4 INR elevation in either group.

Lymphopenia was observed in 47% of NEXAVAR-treated patients and 42% of placebo patients.

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

7.2 Adverse Reactions in RCC Study 1 (Study 11213)

Table 6 shows the percentage of RCC patients experiencing adverse events 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 events were reported in 31% of patients receiving NEXAVAR compared to 22% of patients receiving placebo. CTCAE Grade 4 adverse events were reported in 7% of patients receiving NEXAVAR compared to 6% of patients receiving placebo.

Table 6 : Adverse Reactions Reported in at Least 10% of Patients and at a Higher Rate in NEXAVAR Arm Than the Placebo Arm – RCC Study 1 (Study 11213)

Adverse Reactions NCI-CTCAE v3 Category/Term	NEXAVAR N=451 All Grades %	Grade 3 %	Grade 4 %	Placebo N=451 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 groups (10% of NEXAVAR patients and 8% of placebo patients).

Laboratory Abnormalities

The following laboratory abnormalities were observed in RCC patients in Study 1 (Study 11213):

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 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 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 451patients (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-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.

7.3 Adverse Reactions in DTC Study

The safety of NEXAVAR was evaluated in 416 patients with locally recurrent or metastatic, progressive differentiated thyroid carcinoma (DTC) refractory to radioactive iodine (RAI) treatment randomized to receive 400 mg twice daily NEXAVAR (n=207) or matching placebo (n=209) until disease progression or intolerable toxicity in a double-blind trial *[see Clinical Studies (14.3)]*. The data described below reflect a median exposure to NEXAVAR for 46 weeks (range 0.3 to 135). The population exposed to NEXAVAR was 50% male, and had a median age of 63 years.

Dose interruptions for adverse reactions were required in 66% of patients receiving NEXAVAR and 64% of patients had their dose reduced. Drug-related adverse reactions that resulted in treatment discontinuation were reported in 14% of NEXAVAR-treated patients compared to 1.4% of placebo-treated patients.

Table 7 shows the percentage of DTC patients experiencing adverse reactions at a higher rate in NEXAVAR-treated patients than placebo-treated patients in the double-blind phase of the DTC study. CTCAE Grade 3 adverse reactions occurred in 53% of NEXAVAR-treated patients compared to 23% of placebo-treated patients. CTCAE Grade 4 adverse reactions occurred in 12% of NEXAVAR-treated patients compared to 7% of placebo-treated patients.

Table 7 : Per-Patient Incidence of Selected Adverse Reactions Occurring at a Higher Incidence in NEXAVAR-Treated Patients [Between Arm Difference of ≥ 5% (All Grades)[1] or ≥ 2% (Grades 3 and 4)]

MedDRA Primary System Organ Class & Preferred Term	NEXAVAR N = 207 All Grades (%)	Grades 3 and 4 (%)	Placebo N = 209 All Grades (%)	Grades 3 and 4 (%)
Gastrointestinal disorders				
Diarrhea	68	6	15	1
Nausea	21	0	12	0
Abdominal pain[2]	20	1	7	1
Constipation	16	0	8	0.5
Stomatitis[3]	24	2	3	0
Vomiting	11	0.5	6	0
Oral pain[4]	14	0	3	0
General disorders and administration site conditions				
Fatigue	41	5	20	1
Asthenia	12	0	7	0
Pyrexia	11	1	5	0
Investigations				
Weight loss	49	6	14	1
Metabolism and nutrition disorders				
Decreased appetite	30	2	5	0
Musculoskeletal and connective tissue disorders				
Pain in extremity	15	1	7	0
Muscle spasms	10	0	3	0
Neoplasms benign, malignant and unspecified				
Squamous cell carcinoma of skin	3	3	0	0
Nervous system disorders				
Headache	17	0	6	0
Dysgeusia	6	0	0	0
Respiratory, thoracic and mediastinal disorders				
Dysphonia	13	0.5	3	0
Epistaxis	7	0	1	0
Skin and subcutaneous tissue disorders				
PPES[5]	69	19	8	0
Alopecia	67	0	8	0
Rash	35	5	7	0
Pruritus	20	0.5	11	0
Dry skin	13	0.5	5	0
Erythema	10	0	0.5	0
Hyperkeratosis	7	0	0	0
Vascular disorders				
Hypertension[6]	41	10	12	2

1. National Cancer Institute Common Terminology Criteria for Adverse Events Version 3.0
2. Includes the following terms: abdominal pain, abdominal discomfort, hepatic pain, esophageal pain, esophageal discomfort, abdominal pain lower, abdominal pain upper, abdominal tenderness, abdominal rigidity
3. Includes the following terms: stomatitis, aphthous stomatitis, mouth ulceration, mucosal inflammation
4. Includes the following terms: oral pain, oropharyngeal discomfort, glossitis, burning mouth syndrome, glossodynia
5. Palmar-plantar erythrodysesthesia syndrome (Hand-foot skin reaction)
6. Includes the following terms: hypertension, blood pressure increased, blood pressure systolic increased

Laboratory Abnormalities

Elevated TSH levels are discussed elsewhere in the labeling *[see Warnings and Precautions (6.14)]*. The relative increase for the following laboratory abnormalities observed in NEXAVAR-treated DTC patients as compared to placebo-treated patients is similar to that observed in the RCC and HCC studies: lipase, amylase, hypokalemia, hypophosphatemia, neutropenia, lymphopenia, anemia, and thrombocytopenia *[see Adverse Reactions (7.1, 7.2)]*.

Serum ALT and AST elevations were observed in 59% and 54% of the NEXAVAR-treated patients as compared to 24% and 15% of placebo-treated patients, respectively. High grade (≥ 3) ALT and AST elevations were observed in 4% and 2%, respectively, in the NEXAVAR-treated patients as compared to none of the placebo-treated patients.

Hypocalcemia was more frequent and more severe in patients with DTC, especially those with a history of hypoparathyroidism, compared to patients with RCC or HCC. Hypocalcemia was observed in 36% of DTC patients receiving NEXAVAR (with 10% ≥ Grade 3) as compared with 11% of placebo-treated patients (3% ≥ Grade 3). In the DTC study, serum calcium levels were monitored monthly.

7.4 Additional Data from Multiple Clinical Trials or Though Post-Marketing Use

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

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

Adverse reactions reported in multiple clinical trials or through postmarketing use are listed below in Table 8, by system organ class (in MeDRA) and frequency. Frequencies are defined as: very common (≥ 1/10), common (≥1/100 to < 1/10), uncommon (≥1/1,000 to < 1/100), rare (≥1/10,000 to < 1/1,000), not known (cannot be estimated from the data available).

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

Table 8 : All Adverse Drug Reactions reported in patients in multiple clinical trials or through post-marketing use

System Organ Class	Very Common ≥ 1/10	Common ≥ 1/100 to < 1/10	Uncommon ≥ 1/1,000 to < 1/100	Rare ≥ 1/10,000 to < 1/1000	Not Known
Infections and Infestations	infection	folliculitis			
Blood and Lymphatic System Disorders	lymphopenia	leucopenia neutropenia anaemia thrombocytopenia			
Immune system Disorders			anaphylactic reaction hypersensitivity reactions (including skin reactions and urticaria)		angioedema
Endocrine Disorders		hypothyroidism	hyperthyroidism		
Metabolism and Nutrition Disorders	anorexia hypophosphataemia	hypocalcaemia hypokalemia hyponatraemia	dehydration		
Psychiatric Disorders		depression			
Nervous System Disorders		peripheral sensory neuropathy dysguesia	reversible posterior leukoencephalopathy*		
Ear and Labyrinth Disorders		tinnitus			
Cardiac Disorders		congestive heart failure* myocardial ischemia and/or infarction*		QT prolongation	
Vascular Disorders	hemorrhage (inc. gastrointestinal*, respiratory tract* and cerebral hemorrhage*) hypertension	flushing	hypertensive crisis*		
Respiratory, Thoracic and Mediastinal Disorders		rhinorrhoea dysphonia	interstitial lung disease-like events* (pneumonitis, radiation pneumonitis, acute respiratory distress, interstitial pneumona, pulmonitis and lung inflammatiion etc)		
Gastrointestinal Disorders	diarrhoea nausea vomiting constipation	stomatitis (including dry mouth and glossodynia) dyspepsia dysphagia gastro oesophageal reflux disease	pancreatitis gastritis gastrointestinal perforations*		
Hepato-biliary Disorders			increase in bilirubin and jaundice, cholecystitis, cholangitis	drug induced hepatitis*	
Skin and Subcutaneous Tissue Disorders	dry skin rash alopecia hand-foot skin reaction** pruritus erythema	keratoacanthoma/squamous cell cancer of the skin dermatitis exfoliative acne skin desquamation hyperkeratosis	eczema erythema multiforme		toxic epidermal necrolysis* radiation recall dermatitis leukocytoclastic vasculitis Stevens-Johnson syndrome
Musculoskeletal, Connective Tissue and Bone Disorders	arthralgia	myalgia muscle spasms			rhabdomyolysis
Renal and Genitourinary Disorders		renal failure proteinuria		Nephrotic syndrome	
Reproductive System and Breast Disorders		erectile dysfunction	gynaecomastia		
General Disorders and Administration Site Conditions	fatigue pain (including mouth, abdominal, bone, tumour pain and headache) fever	asthenia influenza like illness mucosal inflammation			
Investigations	increased amylase increased lipase weight decreased	transient increase in transaminases	transient in increase in blood alkaline phosphatase INR abnormal prothrombin level abnormal		

* these adverse reactions may have a life-threatening or fatal outcome. Such events are either uncommon or less frequent than uncommon
** palmar-plantar erythrodysaethesia syndrome in MedDRA

7.5 Additional information on special populations

Two randomized placebo-controlled trials comparing safety and efficacy of sorafenib in combination with doublet platinum-based chemotherapies (carboplatin/paclitaxel and separately gemcitabine/cisplatin) versus the respective doublet platinum-based chemotherapies alone as first-line treatment for patients with advanced Non-Small Cell Lung Carcinoma (NSCLC) did not meet their primary endpoint of improved overall survival. Safety events were generally consistent with those previously reported. However, in both trials, higher mortality was observed in the subset of patients with squamous cell carcinoma of the lung treated with sorafenib and doublet platinum-based chemotherapies versus those treated with doublet platinum-based chemotherapies alone (paclitaxel/carboplatin: HR 1.81, 95% CI 1.19-2.74; gemcitabine/cisplatin: HR 1.22, 95% CI 0.82 – 1.80). No definitive cause was identified for the findings.

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

8 DRUG-DRUG INTERACTIONS

8.1 UGT1A1 and UGT1A9 Substrates

Caution is recommended when administering NEXAVAR with compounds that are metabolized/eliminated predominantly by the UGT1A1 pathway (e.g. irinotecan). In vitro data show that sorafenib inhibits glucuronidation by the UGT1A1 (Ki value: 1 μM) and UGT1A9 (Ki value: 2 μM) pathways. Concomitant clinical administration of NEXAVAR with irinotecan, whose active metabolite SN-38 is further metabolized by the UGT1A1 pathway, resulted in a 67-120% increase in the AUC of SN-38. Systemic exposure to substrates of UGT1A1 and UGT1A9 may increase when co-administered with NEXAVAR.

8.2 Docetaxel

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

8.3 Doxorubicin/Irinotecan

Concomitant treatment with NEXAVAR resulted in a 21% increase in the AUC of doxorubicin. Although the clinical significance of these findings is unknown, caution is recommended when administering doxorubicin with NEXAVAR.

When administered with irinotecan, whose active metabolite SN-38 is further metabolized by the UGT1A1 pathway, there was a 67 120% increase in the AUC of SN-38 and a 26-42% increase in the AUC of irinotecan. The clinical significance of these findings is unknown. (see section Special warnings and precautions for use).

8.4 Fluorouracil

Both increases (21%-47%) and decreases (10%) in the AUC of fluorouracil were observed with concomitant treatment with NEXAVAR. Caution is recommended when NEXAVAR is co-administered with fluorouracil/leucovorin.

8.5 Neomycin

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

8.6 CYP2B6 and CYP2C8 Substrates

Sorafenib inhibits CYP2B6 and CYP2C8 in vitro with Ki values of 6 and 1-2 μM, respectively. In a separate clinical study, concomitant administration of sorafenib with paclitaxel resulted in an increase, instead of a decrease, in the exposure of 6-OH paclitaxel, the active metabolite of paclitaxel that is formed by CYP2C8. These data suggt that sorafenib may not be an in vivo inhibitor of CYP2C8. 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.

8.7 CYP3A4 Inducers

Continuous concomitant administration of NEXAVAR and rifampicin resulted in an average 37% reduction of sorafenib AUC. Other inducers of CYP3A4 activity (e.g. *Hypericum perforatum* also known as St. John's wort, phenytoin, carbamazepine, phenobarbital, and dexamethasone) may also increase metabolism of sorafenib and thus decrease sorafenib concentrations. *[see Dosage and Administration (3)]*.

8.8 CYP3A4 Inhibitors and CYP Isoform Substrates

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, clinical pharmacokinetic interactions of sorafenib with CYP3A4 inhibitors are unlikely.

Studies with human liver microsomes demonstrated that sorafenib is a competitive inhibitor of CYP2C19, CYP2D6, and CYP3A4 as indicated by Ki values of 17 μM, 22 μM, and 29 μM, respectively.

Concomitant clinical administration of midazolam, dextromethorphan, and omeprazole, which are substrates of cytochromes CYP3A4, CYP2D6, and CYP2C19, respectively, following 4 weeks of sorafenib administration did not alter the exposure cyclophosphamide f these agents. This indicates that sorafenib is neither an inhibitor nor an inducer of these cytochrome P450 isoenzymes.

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*.

Studies with human liver microsomes demonstrated that sorafenib is a competitive inhibitor of CYP2C9 with a Ki value of 7-8 μM. The possible effect of sorafenib on 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 and may not be an in vivo inhibitor of CYP2C9. [see Warnings and Precautions (6.7)].

8.9 *In Vitro* Studies: 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. Continuous concomitant clinical administration of sorafenib and rifampicin resulted in an average 37% reduction of sorafenib AUC. Other inducers of CYP3A4 activity (e.g. Hypericum perforatum also known as St. John's wort, phenytoin, carbamazepine, phenobarbital, and dexamethasone) may also increase the metabolism of sorafenib and thus decrease sorafenib concentrations.

8.10 Combination with Other Antineoplastic Agents

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

8.11 Paclitaxel/Carboplatin

Administration of paclitaxel (225 mg/m^2) and carboplatin (AUC = 6) with sorafenib (≤ 400 mg twice daily), administered with a 3-day break in sorafenib dosing around administration of paclitaxel/carboplatin, resulted in no significant effect on the pharmacokinetics of paclitaxel. See Drug Interactions (7.1, 7.2, 7.3 and 7.4) for information about interactions with irinotecan, docetaxel, doxorubicin and fluorouracil/ leucovorin.

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

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

8.12 Capecitabine

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

9 USE IN SPECIFIC POPULATIONS

9.1 Pregnancy

Pregnancy Category D *[see Warnings and Precautions (6.10)]*.

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.

9.2 Women of childbearing-potential

In animals, sorafenib has been shown to be teratogenic and embryotoxic. Adequate contraception should be used during therapy and for at least 2 weeks after completion of therapy (see section WARNINGS AND PRECAUTIONS and PRECLINICAL SAFETY DATA).

9.3 Nursing Mothers

It is not known whether sorafenib is excreted in human milk. In animals, sorafenib and/or its metabolites were excreted in milk. Because many drugs are excreted in human milk and because 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.

9.4 Fertility

Results from animal studies indicate that sorafenib can impair male and female fertility (see section Preclinical safety data).

9.5 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.

9.6 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.

9.7 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 (12.2)].

9.8 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 (12.2)].

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

10 OVER DOSAGE

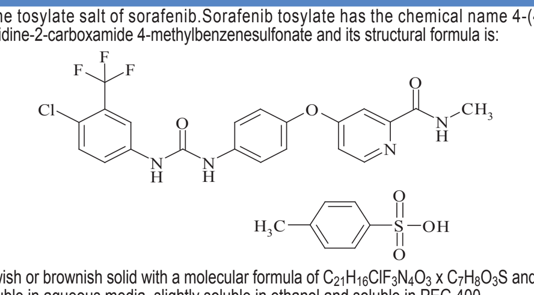
There is no specific treatment for NEXAVAR overdose.

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)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 $C_{21}H_{16}ClF_3N_4O_3 \times C_7H_8O_3S$ 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 sulfate, magnesium stearate, macrogol 3350, titanium dioxide and ferric oxide red.

12 PHARMACOLOGICAL PROPERTIES

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. Sorafenib also inhibited tumor growth of differentiated thyroid carcinoma.

12.2 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 doses of NEXAVAR for 7 days resulted in a 2.5- to 7-fold accumulation compared to single dose. Steady-state plasma sorafenib concentrations are achieved within 7 days, with a peak-to-trough ratio of mean concentrations of less than 2.

The steady-state concentrations of sorafenib following administration of 400 mg NEXAVAR twice daily were evaluated in DTC, RCC and HCC patients. Patients with DTC have mean steady-state concentrations that are 1.8-fold higher than patients with HCC and 2.3-fold higher than those with RCC. The reason for increased sorafenib concentrations in DTC patients is unknown.

Absorption and Distribution

Following oral administration, sorafenib reaches peak plasma levels in approximately 3 hours. When 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 administration 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 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 conjugates may be cleaved in the GI tract by bacterial glucuronidase activity, allowing reabsorption of unconjugated drug. Co-administration of neomycin interferes with this process, decreasing the mean bioavailability of sorafenib by 54%.

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

Pediatric

There are no pharmacokinetic data in pediatric patients.

Hepatic Impairment

Sorafenib is cleared primarily by the liver. In hepatocellular carcinoma (HCC) patients with Child-Pugh A or B (mild to moderate) hepatic impairment, exposure values were comparable and within the range observed in patients without hepatic impairment. The pharmacokinetics (PK) of sorafenib in Child-Pugh A and Child-Pugh B non-HCC patients were similar to the PK in healthy volunteers. The pharmacokinetics of sorafenib have not been studied in patients with severe (Child-Pugh C) hepatic impairment *[see Warnings and Precautions (6.11) and Use in Specific Populations (9.7)]*.

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 a clinical pharmacology study, the pharmacokinetics of sorafenib were evaluated following administration of a single 400 mg dose to subjects with normal renal function, and in subjects with mild (CrCl > 50-80 ml/min), moderate (CrCl 30-50 ml/min), or severe (CrCl < 30 ml/min) renal impairment, not undergoing dialysis. There was no relationship observed between sorafenib exposure and renal function. No dosage adjustment is necessary based on mild, moderate or severe renal impairment not undergoing dialysis *[see Use in Specific Populations (9.8)]*.

12.3 Pharmacodynamics

QT interval prolongation

In a clinical pharmacology study, QT/QTc measurements were recorded in 31 patients at baseline (pre-treatment) and post-treatment. After one 28-day treatment cycle, at the time of maximum concentration of sorafenib, QTcB was prolonged by 4 ±19 msec and QTcF by 9 ±18 msec, as compared to placebo treatment at baseline. No subject showed a QTcB or QTcF >500 msec during the post-treatment ECG monitoring. (see Special warnings and precautions for use)

13 PRECLINICAL SAFETY DATA

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity studies have not been performed with sorafenib.

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

Repeat-dose toxicity studies revealed changes (degenerations and regenerations) in various organs at exposures below the anticipated clinical exposure (based on AUC comparisons).

After repeated dosing to young and growing dogs effects on bone and teeth were observed at exposures below the clinical exposure. Changes consisted in irregular thickening of the femoral growth plate, hypocellularity of the bone marrow next to the altered growth plate, and alterations of the dentin composition. Similar effects were not induced in adult dogs.

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

No specific studies with sorafenib have been conducted in animals to evaluate the effect on fertility. An adverse effect on male and female fertility can however be expected because repeat-dose studies in animals have shown changes in male and female reproductive organs at exposures below the anticipated clinical exposure (based on AUC).Typical changes consisted of signs of degeneration and retardation in testes, epididymides, prostate, and seminal vesicles of rats. Female rats showed central necrosis of the corpora lutea and arrested follicular development in the ovaries. Dogs showed tubular degeneration in the testes at 600 mg/m2/day,and oligospermia at 1200 mg/m2/day of sorafenib.

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

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), renal cell carcinoma (RCC) and differentiated thyroid carcinoma (DTC).

14.1 Hepatocellular Carcinoma

The **HCC Study 1 (Study 100554)** 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 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 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%) (see Table 9).

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 10 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 10).

Table 9. Baseline Cancer Characteristics; subjects valid for ITT population

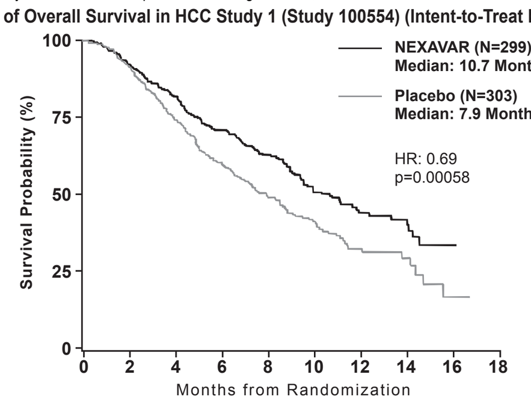
	Placebo (n=303)	Sorafenib (n=299)
Child-Pugh Status n (%)		
A	297 (98%)	284 (95%)
B	6 (2%)	14 (5%)
C	0 (0%)	1 (0.3%)
Hepatitis from Laboratory n (%)		
Hepatitis C only	81 (27%)	86 (29%)
Hepatitis B only	28 (9%)	32 (11%)
Hepatitis B & C	3 (1%)	7 (2%)
Negative serology for HCV Ab or HBs Ag	165 (55%)	149 (50%)
Missing	26 (9%)	25 (8%)

Table 10 : Efficacy Results from HCC Study 1 (Study 100554)

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

CI=Confidence interval
1. Hazard ratio, sorafenib/placebo, stratified Cox model
2. Stratified logrank (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 1 (Study 100554) (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

There were 168 patients (28%) of 602 patients in Study 100554 progressed from Child-Pugh A to Child-Pugh B or C measured from baseline, was apparently shorter for sorafenib than placebo (47 days vs. 84 days), the median OS (257 days vs. 171 days) and TTP (126 days vs. 80 days) were longer for sorafenib than placebo which both OS and TTP were the most important endpoints after treatment (see Table 11). From the published paper of Albou-Alfa, Child-Pugh B patients treated with NEXAVAR have more cases of hyperbilirubinemia, encephalopathy and ascites. Please refer to the references for details. (G. K. Albou-Alfa et al. Is sorafenib safe and effective in patients with hepatocellular carcinoma (HCC) and Child-Pugh B (CPB) cirrhosis? Journal of Clinical Oncology. 2008 ASCO Annual Meeting Proceedings (Post-Meeting Edition). Vol 26, No 15S (May 20 Supplement) 2008: 4518.

Table 11. Subjects post baseline Child-Pugh B or C

	Placebo (n=73)	Sorafenib (n=95)
Baseline Characteristics		
Child-Pugh Status, (n)		
A	72	85
B	1	10
Etiology, (n)		
Alcohol	17	31
Hepatitis B only	12	14
Hepatitis C only	19	26
Others	11	8
Unknown	14	16
Number reached Child-Pugh B, (n)	71	88
Number reached Child-Pugh C, (n)	2	7
Median time to Child-Pugh B or C measured from baseline	84 days	47 days
Median time on treatment after achieving status Child-Pugh B or C	22 days	48 days
Median OS in these subjects	**171 days**	**257 days**
TTP (based on independent review)	**80 days**	**126 days**
6-month OS rate	46%	62%
Radiological progression-free rate at 3 months	38%	60%
Radiological progression-free rate at 6 months	13%	41%

The HCC Study 2 (study 11849) was a Phase III, international, multi-centre, randomized, double blind, placebo-controlled study in 226 patients with hepatocellular carcinoma in China, Taiwan and Korea. All the 226 randomized subjects were Asians. Of the 226 randomized subjects, 76 subjects were randomized to placebo and 150 subjects were randomized to NEXAVAR.

Analysis of efficacy data revealed that NEXAVAR significantly prolonged OS compared with placebo (HR: 0.68, p= 0.014). The analysis of TTP also reveals a significant and meaningful improvement in favor of NEXAVAR. Median TTP was 41.5 days for placebo subjects compared to 84 days for NEXAVAR subjects (HR: 0.57, p< 0.001) (see Table 12).

Table 12: Efficacy Results from HCC study 2 (study 11849)

Efficacy Parameter	Nexavar (N=150)	Placebo (N=76)	P-value	HR (95% CI)
Overall survival (OS) [median, days (95% CI)]	198 (169, 230)	127 (114, 166)	0.014	0.68 (0.50, 0.93)
Time to Progression, (TTP) [median, days (95% CI)]**	84 (80, 109)	41.5 (41, 47)	< 0.001	0.57 (0.42, 0.79)

CI= Confidence interval, HR= Hazard ratio (NEXAVAR over placebo)

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 (Study 11213) 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 13 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.

Table 13 : Demographic and Disease Characteristics – RCC Study 1 (Study 11213)

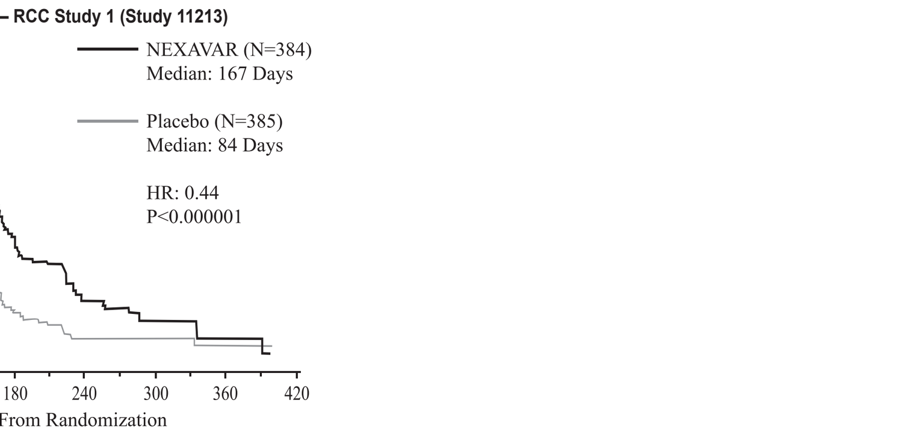
Characteristics	NEXAVAR N=384 n	(%)	Placebo N=385 n	(%)
Gender				
Male	267	(70)	287	(75)
Female	116	(30)	98	(25)
Race				
White	276	(72)	278	(73)
Black/Asian/Hispanic/Other	11	(3)	10	(2)
Not reported[a]	97	(25)	97	(25)
Age group				
<65	255	(67)	280	(73)
≥65	127	(33)	103	(27)
ECOG performance status 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 (Study 11213)



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 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.

RCC Study 2 (Study 100391) 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 group (163 days) than in the placebo group (41 days) (p=0.0001, HR=0.29).

14.3 Differentiated Thyroid Carcinoma

The safety and effectiveness of NEXAVAR was established in a multicenter, randomized (1:1), double-blind, placebo-controlled trial conducted in 417 patients with locally recurrent or metastatic, progressive differentiated thyroid carcinoma (DTC) refractory to radioactive iodine (RAI) treatment. Randomization was stratified by age (< 60 years versus ≥ 60 years) and geographical region (North America, Europe, and Asia).

All patients were required to have actively progressing disease defined as progression within 14 months of enrollment. RAI-refractory disease was defined based on four criteria that were not mutually exclusive. All RAI treatments and diagnostic scans were to be performed under conditions of a low iodine diet and adequate TSH stimulation. Following are the RAI-refractory criteria and the proportion of patients in the study that met each one: a target lesion with no iodine uptake on RAI scan (68%); tumors with iodine uptake and progression after RAI treatment within 16 months of enrollment (12%); tumors with iodine uptake and multiple RAI treatments with the last treatment greater than 16 months prior to enrollment, and disease progression after each of two RAI treatments administered within 16 months of each other (7%); cumulative RAI dose ≥ 600 mCi administered (34%). The major efficacy outcome measure was progression-free survival (PFS) as determined by a blinded, independent radiological review using a modified Response Evaluation Criteria in Solid Tumors v. 1.0 (RECIST). RECIST was modified by inclusion of clinical progression of bone lesions based on the need for external beam radiation (4.4% of progression events). Additional efficacy outcomes measures included overall survival (OS), tumor response rate, and duration of response.

Patients were randomized to receive NEXAVAR 400 mg twice daily (n=207) or placebo (n=210). Of the 417 patients randomized, 48% were male, the median age was 63 years, 61% were 60 years or older, 60% were white, 62% had an ECOG performance status of 0, and 99% had undergone thyroidectomy. The histological diagnoses were papillary carcinoma in 57%, follicular carcinoma (including Hürthle cell) in 25%, and poorly differentiated carcinoma in 10%, and other in 8% of the study population. Metastases were present in 96% of the patients: lungs in 86%, lymph nodes in 51%, and bone in 27%. The median cumulative RAI activity administered prior to study entry was 400 mCi.

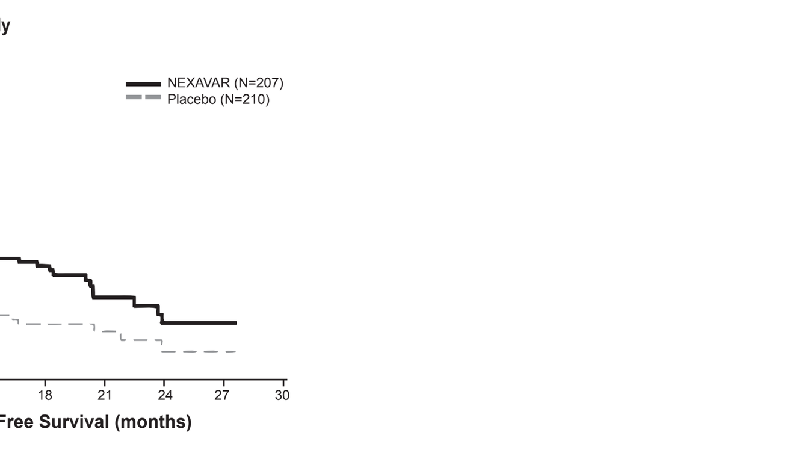
A statistically significant prolongation in PFS was demonstrated among NEXAVAR-treated patients compared to those receiving placebo. Following investigator-determined disease progression, 157 (75%) patients randomized to placebo crossed over to open-label NEXAVAR, and 61 (30%) patients randomized to NEXAVAR received open-label NEXAVAR. There was no statistically significant difference in overall survival between the two treatment arms (see Table 14 and Figure 3).

Table 14. Efficacy Results from Study in Differentiated Thyroid Carcinoma

	NEXAVAR N=207	Placebo N=210
Progression-free Survival [1]		
Number of Deaths or Progression	113 (55%)	136 (65%)
Median PFS in Months (95% CI)	10.8 (9.1, 12.9)	5.8 (5.3, 7.8)
Hazard Ratio (95% CI)	0.59 (0.46, 0.76)	
P-value[2]	<0.001	
Overall Survival [3]		
Number of Deaths	66 (32%)	72 (34%)
Median OS in Months (95% CI)	NR	36.5 (32.2, NR)
Hazard Ratio (95% CI)	0.88 (0.63, 1.24)	
P-value [2]	0.47	
Objective Response		
Number of Objective Responders [4]	24 (12%)	1 (0.5%)
(95%CI)	(7.6%, 16.8%)	(0.01%, 2.7%)
Median Duration of Response in Months (95% CI)	10.2 (7.4, 16.6)	NE

1 Independent radiological review
2 Two-sided log-rank test stratified by age (< 60 years, ≥ 60 years) and geographic region (North America,Europe, Asia)
3 Conducted 9 months after the data cut-off for the final PFS analysis
4 All objective responses were partial responses
NR = Not Reached, CI = Confidence interval, NE = Not Estimable

Figure 3: Kaplan-Meier Curve of Progression-Free Survival in DTC Study



Patients at Risk										
NEXAVAR	207	159	115	91	60	35	27	13	5	2
Placebo	210	135	78	55	36	14	9	6	2	2

15 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

List of excipients

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

Film-coat: hypromellose, macrogol3350, titanium dioxide, iron oxide red.

Storage

8-1000 tablets Aluminum blister per box.

Store below 30°C in a dry place. Keep out of the reach of children.

16 PATIENT COUNSELING INFORMATION

16.1 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 and/or infarction *[see Warnings and Precautions (6.1)]*.

16.2 Bleeding

Inform patients that NEXAVAR can increase the risk of bleeding and that they should promptly report any episodes of bleeding.

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 (6.7)]*.

16.3 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 (6.4 and 6.5)]*

16.4 Skin Reactions

Advise patients of the possible occurrence of hand-foot skin reaction and rash during NEXAVAR treatment and appropriate countermeasures.

16.5 Gastrointestinal Perforation

Advise patients that cases of gastrointestinal perforation have been reported in patients taking NEXAVAR *[see Warnings and Precautions (6.3 and 6.6)]*.

16.6 Wound Healing Complications

Inform patients that temporary interruption of NEXAVAR is recommended in patients undergoing major surgical procedures *[see Warnings and Precautions (6.8)]*.

16.7 QT Interval Prolongation

Inform patients with a history of prolonged QT interval that NEXAVAR can worsen the condition *[see Warnings and Precautions (6.2)]*.

16.8 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 (6.10), Use in Specific Populations (9.1)]*.

16.9 Nursing Mothers

Advise mothers not to breast-feed while taking NEXAVAR *[see Use in Specific Populations (9.3)]*.

16.10 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.

Bayer AG, Kaiser-Wilhelm-Allee, 51368 Leverkusen, Germany

NEXAVAR film-coated tablets 200mg / USPI_11/2013 + CCDS21_12Jun2013/TW11