蕾莎瓦® 膜衣錠 200毫克

Nexavar® film-coated tablets 200 mg

衛署藥製字第042727號
本藥須由醫師處方使用

1. 品名

蕾莎瓦®膜衣錠200毫克

2. 組成

21.4 種性成分為甲苯磺酸鹽形式的活性不溶分布部分構成為膜衣錠芯之成份相對和無活性的膜衣錠(HCC)，且用為ChilP Pugh class A患者。
2.2 此製劑無偏心形狀(如：橢圓形或長條形)或凹槽(scoreforeso-alpha)或凸起(convex)的設計，尺寸適合口服吞服物法使之處方。
2.3 此劑活性藥治療無法或不耐受抗癌藥物治療的進行性(progressive)分化型肝細胞癌(HTC)。

3. 臨床與使用方法

Nexavar的每日建議劑量為一片400毫克(200毫克)服用的，一天服用2次，不食食物一起服用(食少用量前一小時或用餐後2小時)；口服使用，以水吞服；治療過程直到病患無法再得到臨床益處發生不可接受的毒性。

預期臨床效果與無效的假設測試方式

處理疑似腫瘤的長處時，可考慮使用Nexavar的藥/處方劑量，當必須要為減少劑量時，Nexavar的劑量應降至每天400毫克，若需進一步減少劑量，Nexavar的劑量可以降至每天400毫克(參見警語和注意事項6)。
因皮膚毒性的劑量調整的建議如下表(附件2)：

表1：即加速度智加劑量疗程的劑量調整建議

皮膚毒性分級	療法	Nexavar劑量調整
第1級：痛感、感覺異常、刺痛、麻痛感覺、紅斑或皮膚脫屑不影響無法使用正常活動	任何疗程	持續Nexavar治療並考慮局部治療以緩解症狀
第2級：疼痛的紅斑或手或脚的膜炎/或皮膚脫屑影響正常活動	第一次發生	持續Nexavar治療並考慮局部治療以緩解症狀並先內服抗生素治療
	第二次再次出現皮膚毒性反應	中斷Nexavar治療，直到毒性改善到第0-1級，並以原劑量的一半重新開始Nexavar治療，如果Nexavar的劑量可降至400毫克/天，則繼續治療；或考慮終止Nexavar治療
	第三次再次出現皮膚毒性反應	停止Nexavar治療
第3級：深度脫皮、潰瘍、或潰瘍或手或脚的膜炎影響正常活動，或潰瘍的非感染性蜂窩織炎需要全身抗生素治療	第一次或第二次發生	中斷Nexavar治療，直到毒性改善到第0-1級，並以原劑量的一半重新開始Nexavar治療，如果Nexavar的劑量可降至400毫克/天，則繼續治療；或考慮終止Nexavar治療
	第三次發生	停止Nexavar治療

分化型肝癌藥劑的劑量調整方式：

表2：分化型肝癌藥劑的劑量調整方式

皮膚毒性分級	療法	Nexavar劑量調整
第1級：痛感、感覺異常、刺痛、麻痛感覺、紅斑或皮膚脫屑不影響無法使用正常活動	任何疗程	持續NEXAVAR治療
第2級：疼痛的紅斑或手或脚的膜炎影響正常活動	第1次發生	持續NEXAVAR的劑量至每天600毫克；若7天內沒有進步改善，請暫停治療，直到毒性改善到第0-1級，如果第二次出現皮膚毒性反應，請暫停治療，直到毒性改善到第0-1級，如果第三次出現皮膚毒性反應，請暫停治療，直到毒性改善到第0-1級，如果第四次出現皮膚毒性反應，請暫停治療，直到毒性改善到第0-1級，如果第五次出現皮膚毒性反應，請暫停治療，直到毒性改善到第0-1級，如果第六次出現皮膚毒性反應，請暫停治療，直到毒性改善到第0-1級，如果第七次出現皮膚毒性反應，請暫停治療，直到毒性改善到第0-1級，如果第八次出現皮膚毒性反應，請暫停治療，直到毒性改善到第0-1級，如果第九次出現皮膚毒性反應，請暫停治療，直到毒性改善到第0-1級，如果第十次出現皮膚毒性反應，請暫停治療，直到毒性改善到第0-1級，如果第十一次出現皮膚毒性反應，請暫停治療，直到毒性改善到第0-1級，如果第十二次出現皮膚毒性反應，請暫停治療，直到毒性改善到第0-1級，如果第十三次出現皮膚毒性反應，請暫停治療，直到毒性改善到第0-1級，如果第十四次出現皮膚毒性反應，請暫停治療，直到毒性改善到第0-1級，如果第十五次出現皮膚毒性反應，請暫停治療，直到毒性改善到第0-1級，如果第十六次出現皮膚毒性反應，請暫停治療，直到毒性改善到第0-1級，如果第十七次出現皮膚毒性反應，請暫停治療，直到毒性改善到第0-1級，如果第十八次出現皮膚毒性反應，請暫停治療，直到毒性改善到第0-1級，如果第十九次出現皮膚毒性反應，請暫停治療，直到毒性改善到第0-1級，如果第二十次出現皮膚毒性反應，請暫停治療，直到毒性改善到第0-1級，如果第二十一次出現皮膚毒性反應，請暫停治療，直到毒性改善到第0-1級，如果第二十二次出現皮膚毒性反應，請暫停治療，直到毒性改善到第0-1級，如果第二十三次出現皮膚毒性反應，請暫停治療，直到毒性改善到第0-1級，如果第二十四次出現皮膚毒性反應，請暫停治療，直到毒性改善到第0-1級，如果第二十五次出現皮膚毒性反應，請暫停治療，直到毒性改善到第0-1級，如果第二十六次出現皮膚毒性反應，請暫停治療，直到毒性改善到第0-1級，如果第二十七次出現皮膚毒性反應，請暫停治療，直到毒性改善到第0-1級，如果第二十八次出現皮膚毒性反應，請暫停治療，直到毒性改善到第0-1級，如果第二十九次出現皮膚毒性反應，請暫停治療，直到毒性改善到第0-1級，如果第三十次出現皮膚毒性反應，請暫停治療，直到毒性改善到第0-1級，如果第三十一次出現皮膚毒性反應，請暫停治療，直到毒性改善到第0-1級，如果第三十二次出現皮膚毒性反應，請暫停治療，直到毒性改善到第0-1級，如果第三十三次出現皮膚毒性反應，請暫停治療，直到毒性改善到第0-1級，如果第三十四次出現皮膚毒性反應，請暫停治療，直到毒性改善到第0-1級，如果第三十五次出現皮膚毒性反應，請暫停治療，直到毒性改善到第0-1級，如果第三十六次出現皮膚毒性反應，請暫停治療，直到毒性改善到第0-1級，如果第三十七次出現皮膚毒性反應，請暫停治療，直到毒性改善到第0-1級，如果第三十八次出現皮膚毒性反應，請暫停治療，直到毒性改善到第0-1級，如果第三十九次出現皮膚毒性反應，請暫停治療，直到毒性改善到第0-1級，如果第四十次出現皮膚毒性反應，請暫停治療，直到毒性改善到第0-1級，如果第四十一次出現皮膚毒性反應，請暫停治療，直到毒性改善到第0-1級，如果第四十二次出現皮膚毒性反應，請暫停治療，直到毒性改善到第0-1級，如果第四十三次出現皮膚毒性反應，請暫停治療，直到毒性改善到第0-1級，如果第四十四次出現皮膚毒性反應，請暫停治療，直到毒性改善到第0-1級，如果第四十五次出現皮膚毒性反應，請暫停治療，直到毒性改善到第0-1級，如果第四十六次出現皮膚毒性反應，請暫停治療，直到毒性改善到第0-1級，如果第四十七次出現皮膚毒性反應，請暫停治療，直到毒性改善到第0-1級，如果第四十八次出現皮膚毒性反應，請暫停治療，直到毒性改善到第0-1級，如果第四十九次出現皮膚毒性反應，請暫停治療，直到毒性改善到第0-1級，如果第五十次出現皮膚毒性反應，請暫停治療，直到毒性改善到第0-1級，如果第五十一次出現皮膚毒性反應，請暫停治療，直到毒性改善到第0-1級，如果第五十二次出現皮膚毒性反應，請暫停治療，直到毒性改善到第0-1級，如果第五十三次出現皮膚毒性反應，請暫停治療，直到毒性改善到第0-1級，如果第五十四次出現皮膚毒性反應，請暫停治療，直到毒性改善到第0-1級，如果第五十五次出現皮膚毒性反應，請暫停治療，直到毒性改善到第0-1級，如果第五十六次出現皮膚毒性反應，請暫停治療，直到毒性改善到第0-1級，如果第五十七次出現皮膚毒性反應，請暫停治療，直到毒性改善到第0-1級，如果第五十八次出現皮膚毒性反應，請暫停治療，直到毒性改善到第0-1級，如果第五十九次出現皮膚毒性反應，請暫停治療，直到毒性改善到第0-1級，如果第六十次出現皮膚毒性反應，請暫停治療，直到毒性改善到第0-1級，如果第六十一次出現皮膚毒性反應，請暫停治療，直到毒性改善到第0-1級，如果第六十二次出現皮膚毒性反應，請暫停治療，直到毒性改善到第0-1級，如果第六十三次出現皮膚毒性反應，請暫停治療，直到毒性改善到第0-1級，如果第六十四次出現皮膚毒性反應，請暫停治療，直到毒性改善到第0-1級，如果第六十五次出現皮膚毒性反應，請暫停治療，直到毒性改善到第0-1級，如果第六十六次出現皮膚毒性反應，請暫停治療，直到毒性改善到第0-1級，如果第六十七次出現皮膚毒性反應，請暫停治療，直到毒性改善到第0-1級，如果第六十八次出現皮膚毒性反應，請暫停治療，直到毒性改善到第0-1級，如果第六十九次出現皮膚毒性反應，請暫停治療，直到毒性改善到第0-1級，如果第七十次出現皮膚毒性反應，請暫停治療，直到毒性改善到第0-1級，如果第七十一次出現皮膚毒性反應，請暫停治療，直到毒性改善到第0-1級，如果第七十二次出現皮膚毒性反應，請暫停治療，直到毒性改善到第0-1級，如果第七十三次出現皮膚毒性反應，請暫停治療，直到毒性改善到第0-1級，如果第七十四次出現皮膚毒性反應，請暫停治療，直到毒性改善到第0-1級，如果第七十五次出現皮膚毒性反應，請暫停治療，直到毒性改善到第0-1級，如果第七十六次出現皮膚毒性反應，請暫停治療，直到毒性改善到第0-1級，如果第七十七次出現皮膚毒性反應，請暫停治療，直到毒性改善到第0-1級，如果第七十八次出現皮膚毒性反應，請暫停治療，直到毒性改善到第0-1級，如果第七十九次出現皮膚毒性反應，請暫停治療，直到毒性改善到第0-1級，如果第八十次出現皮膚毒性反應，請暫停治療，直到毒性改善到第0-1級，如果第八十一次出現皮膚毒性反應，請暫停治療，直到毒性改善到第0-1級，如果第八十二次出現皮膚毒性反應，請暫停治療，直到毒性改善到第0-1級，如果第八十三次出現皮膚毒性反應，請暫停治療，直到毒性改善到第0-1級，如果第八十四次出現皮膚毒性反應，請暫停治療，直到毒性改善到第0-1級，如果第八十五次出現皮膚毒性反應，請暫停治療，直到毒性改善到第0-1級，如果第八十六次出現皮膚毒性反應，請暫停治療，直到毒性改善到第0-1級，如果第八十七次出現皮膚毒性反應，請暫停治療，直到毒性改善到第0-1級，如果第八十八次出現皮膚毒性反應，請暫停治療，直到毒性改善到第0-1級，如果第八十九次出現皮膚毒性反應，請暫停治療，直到毒性改善到第0-1級，如果第九十次出現皮膚毒性反應，請暫停治療，直到毒性改善到第0-1級，如果第九十一次出現皮膚毒性反應，請暫停治療，直到毒性改善到第0-1級，如果第九十二次出現皮膚毒性反應，請暫停治療，直到毒性改善到第0-1級，如果第九十三次出現皮膚毒性反應，請暫停治療，直到毒性改善到第0-1級，如果第九十四次出現皮膚毒性反應，請暫停治療，直到毒性改善到第0-1級，如果第九十五次出現皮膚毒性反應，請暫停治療，直到毒性改善到第0-1級，如果第九十六次出現皮膚毒性反應，請暫停治療，直到毒性改善到第0-1級，如果第九十七次出現皮膚毒性反應，請暫停治療，直到毒性改善到第0-1級，如果第九十八次出現皮膚毒性反應，請暫停治療，直到毒性改善到第0-1級，如果第九十九次出現皮膚毒性反應，請暫停治療，直到毒性改善到第0-1級，如果第一百次出現皮膚毒性反應，請暫停治療，直到毒性改善到第0-1級，如果第一百一次出現皮膚毒性反應，請暫停治療，直到毒性改善到第0-1級，如果第一百二次出現皮膚毒性反應，請暫停治療，直到毒性改善到第0-1級，如果第一百三次出現皮膚毒性反應，請暫停治療，直到毒性改善到第0-1級，如果第一百四次出現皮膚毒性反應，請暫停治療，直到毒性改善到第0-1級，如果第一百五次出現皮膚毒性反應，請暫停治療，直到毒性改善到第0-1級，如果第一百六次出現皮膚毒性反應，請暫停治療，直到毒性改善到第0-1級，如果第一百七次出現皮膚毒性反應，請暫停治療，直到毒性改善到第0-1級，如果第一百八次出現皮膚毒性反應，請暫停治療，直到毒性改善到第0-1級，如果第一百九次出現皮膚毒性反應，請暫停治療，直到毒性改善到第0-1級，如果第二百次出現皮膚毒性反應，請暫停治療，直到毒性改善到第0-1級，如果第二百一次出現皮膚毒性反應，請暫停治療，直到毒性改善到第0-1級，如果第二百二次出現皮膚毒性反應，請暫停治療，直到毒性改善到第0-1級，如果第二百三次出現皮膚毒性反應，請暫停治療，直到毒性改善到第0-1級，如果第二百四次出現皮膚毒性反應，請暫停治療，直到毒性改善到第0-1級，如果第二百五次出現皮膚毒性反應，請暫停治療，直到毒性改善到第0-1級，如果第二百六次出現皮膚毒性反應，請暫停治療，直到毒性改善到第0-1級，如果第二百七次出現皮膚毒性反應，請暫停治療，直到毒性改善到第0-1級，如果第二百八次出現皮膚毒性反應，請暫停治療，直到毒性改善到第0-1級，如果第二百九次出現皮膚毒性反應，請暫停治療，直到毒性改善到第0-1級，如果第三百次出現皮膚毒性反應，請暫停治療，直到毒性改善到第0-1級，如果第三百一次出現皮膚毒性反應，請暫停治療，直到毒性改善到第0-1級，如果第三百二次出現皮膚毒性反應，請暫停治療，直到毒性改善到第0-1級，如果第三百三次出現皮膚毒性反應，請暫停治療，直到毒性改善到第0-1級，如果第三百四次出現皮膚毒性反應，請暫停治療，直到毒性改善到第0-1級，如果第三百五次出現皮膚毒性反應，請暫停治療，直到毒性改善到第0-1級，如果第三百六次出現皮膚毒性反應，請暫停治療，直到毒性改善到第0-1級，如果第三百七次出現皮膚毒性反應，請暫停治療，直到毒性改善到第0-1級，如果第三百八次出現皮膚毒性反應，請暫停治療，直到毒性改善到第0-1級，如果第三百九次出現皮膚毒性反應，請暫停治療，直到毒性改善到第0-1級，如果第四百次出現皮膚毒性反應，請暫停治療，直到毒性改善到第0-1級，如果第四百一次出現皮膚毒性反應，請暫停治療，直到毒性改善到第0-1級，如果第四百二次出現皮膚毒性反應，請暫停治療，直到毒性改善到第0-1級，如果第四百三次出現皮膚毒性反應，請暫停治療，直到毒性改善到第0-1級，如果第四百四次出現皮膚毒性反應，請暫停治療，直到毒性改善到第0-1級，如果第四百五次出現皮膚毒性反應，請暫停治療，直到毒性改善到第0-1級，如果第四百六次出現皮膚毒性反應，請暫停治療，直到毒性改善到第0-1級，如果第四百七次出現皮膚毒性反應，請暫停治療，直到毒性改善到第0-1級，如果第四百八次出現皮膚毒性反應，請暫停治療，直到毒性改善到第0-1級，如果第四百九次出現皮膚毒性反應，請暫停治療，直到毒性改善到第0-1級，如果第五百次出現皮膚毒性反應，請暫停治療，直到毒性改善到第0-1級，如果第五百一次出現皮膚毒性反應，請暫停治療，直到毒性改善到第0-1級，如果第五百二次出現皮膚毒性反應，請暫停治療，直到毒性改善到第0-1級，如果第五百三次出現皮膚毒性反應，請暫停治療，直到毒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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 Child-Pugh Class A patients with metastatic or unresectable advanced hepatocellular carcinoma (HCC) and inappropriate to local treatment or local treatment failure.

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 radioiodine treatment.

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)
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 perform activities of daily living	4th occurrence	Discontinue NEXAVAR treatment
	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 Carcinoma

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 (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	400 mg daily dose: 200 mg twice daily (1 tablet twice daily)
Second Dose Reduction	400 mg daily dose: 200 mg twice daily (1 tablet twice daily)
Third Dose Reduction	200 mg twice daily: 200 mg once daily (1 tablet once daily)

When dose reduction is necessary for dermatology toxicities, reduce the NEXAVAR dose as indicated in Tabbt 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 by one level (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 two dose levels (see Table 2)
	2nd occurrence	Interrupt NEXAVAR until resolved or improved to grade 1 If 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, rifapentine, 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.
- NEXAVAR in combination with carboplatin and paclitaxel is contraindicated in patients with squamous cell lung cancer [*see 4 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 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 Clinical Studies (14.1)].

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 mIU/L. Elevation of TSH level above 0.5 mIU/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 mIU/L and 25% had TSH levels greater than or equal to 2 mIU/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). Monitoring for keratinocyte carcinomas should be carried out before treatment with NEXAVAR and continued at regular intervals during 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 labelling:

- Cardiac ischemia and 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 40.6% of NEXAVAR-treated patients and 39% 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*	NEXAVAR N=202				Placebo N=202			
NCI– CTCAE v3 Category/Term	Any Grade %	Grade 3 %	Grade 4 %	All Grades %	Grade 3 %	Grade 4 %
Any Event	98	39	40	96	24	39
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	11	<1	0	10	<1	0
Hand-foot skin reaction	21	8	0	3	<1	0
Dry skin	10	0	0	4	0	0
Alopecia	14	0	0	3	0	0
Gastrointestinal						
Diarrhea	55	10	<1	25	2	0
Anorexia	19	1	0	8	<1	0
Nausea	24	1	0	20	3	0
Vomiting	15	2	0	11	2	0
Constipation	12	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 hypertension on either treatment arm.

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: 1% NEXAVAR and 3% placebo and CTCAE grade 4: 0% 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 (23% of NEXAVAR patients and 8% 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	NEXAVAR (N = 149)			Placebo (N = 75)		
System organ class / Preferred term	All Grades %	Grade 3 %	Grade 4 %	All Grades %	Grade 3 %	Grade 4 %
Blood/Bone Marrow						
Hemoglobin	20	4	4	15	0	0
Leukocytes	11	1	0	8	4	0
Platelets	22	1	0	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	0	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	7	0	0
Gastrointestinal						
Anorexia	31	3	0	17	3	0
Ascites	26	7	0	17	9	0
Diarrhea	42	2	0	16	0	0
Metabolic/Laboratory						
Alkaline phosphatase	26	4	0	9	1	0
ALT	32	5	1	24	7	0
AST	41	18	1	31	15	0
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	0	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 HCC 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 treated with NEXAVAR compared to 5% 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-treated patients. Grade 3 or 4 hypoalbuminemia occurred in 1% of each 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 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	NEXAVAR N=451			Placebo N=451		
NCI-CTCAE v3 Category/Term	All Grades %	Grade 3 %	Grade 4 %	All Grades %	Grade 3 %	Grade 4 %
Any Adverse Reactions	95	31	7	88	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 – at sites	15	2	0	8	1	0
Pain						
Pain, abdomen	11	2	0	9	2	0
Pain, joint	10	2	0	7	<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 (CTCAE Grade 2).

Lymphopenia was observed in 28% 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 3% 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 no patients in the placebo treated group.

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 radioiodine 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 for NEXAVAR of 29 months (range 0.3 to 39). The population was 50% male, 96% white, and ECOG PS 0 (100%), median age 63 years, range 15 to 85 years, 2% had received prior kinase inhibitor therapy.

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 study. Grade 3 adverse reactions occurred in 33% 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) or ≥ 2% (Grades 3 and 4))

MedDRA Primary System Organ Class & Preferred Term	NEXAVAR N = 207			Placebo N = 209		
	All Grades (%)	Grades 3 and 4 (%)	Grades 3 and 4 (%)	All Grades (%)	Grades 3 and 4 (%)	Grades 3 and 4 (%)
Gastrointestinal disorders						
Diarrhea	56	2	0	12	0	0
Nausea	21	0	0	12	0	0
Abdominal pain[a]	20	1	0	7	1	0
Constipation	14	0	0	9	0	0
Stomatitis[b]	24	2	0	3	0	0
Vomiting	11	0.5	0	6	0	0
Oral pain[c]	14	0	0	3	0	0
General disorders and administration site conditions						
Fatigue	51	5	0	20	1	0
Asthenia	12	0	0	7	0	0
Pyrexia	11	0	0	5	0	0
Investigations						
Weight loss	49	6	0	14	1	0
Metabolism and nutrition disorders						
Decreased appetite	30	2	0	5	0	0
Musculoskeletal and connective tissue disorders						
Pain in extremity	15	0	0	7	0	0
Muscle spasms	10	0	0	3	0	0
Neoplasms benign, malignant and unspecified						
Squamous cell carcinoma of skin	3	3	0	0	0	0
Nervous system disorders						
Headache	17	0	0	6	0	0
Dysgeusia	6	0	0	2	0	0
Respiratory, thoracic and mediastinal disorders						
Dysphonia	13	0.5	0	3	0	0
Dyspnea	7	0	0	1	0	0
Skin and subcutaneous tissue disorders						
PPES[d]	69	19	0	2	0	0
Alopecia	67	2	0	4	0	0
Rash	35	5	0	7	0	0
Pruritus	20	1	0	4	0	0
Dry skin	13	0.5	0	5	0	0
Erythema	10	0	0.5	0	0	0
Hyperkeratosis	10	1	0	1	0	0
Vascular disorders						
Hypertension[e]	41	10	0	12	2	0

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, lower abdominal pain, abdominal tenderness, epigastric pain
3. Includes the following terms: stomatitis, aphthous stomatitis, mouth ulceration, mucosal inflammation
4. Includes the following terms: oral pain, glossodynia, gingivitis, gingivitis ulcerative, glossitis, glossodynia
5. Palmar-plantar erythrodysesthesia syndrome (Hand-foot skin reaction)
6. Includes the following terms: hypertension, 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.