NEW ZEALAND DATA SHEET

1 PRODUCT NAME

NEXAVAR® Sorafenib tosilate 274 mg (equivalent to sorafenib 200 mg) film-coated tablet

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

NEXAVAR is a multikinase inhibitor targeting several serine/threonine and receptor tyrosine kinases.

For the full list of Excipients, see section 6.1 List of excipients.

3 PHARMACEUTICAL FORM

NEXAVAR tablets contain 200 mg of sorafenib (274 mg sorafenib tosilate). The tablets are film coated red round, faceted biconvex marked with a Bayer cross on one side and "200" on the other.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Hepatocellular carcinoma

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

Renal cell carcinoma

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

Differentiated Thyroid carcinoma

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

4.2 Dose and method of administration

Use in Adults

Recommended dose

The recommended daily dose of NEXAVAR is 400 mg (2 x 200 mg tablets) taken twice a day, either without food or together with a moderate fat meal.

Duration of treatment

Treatment should be continued until the patient is no longer clinically benefiting from therapy or until unacceptable toxicity occurs.

Dose titration, dose adjustment, special monitoring advice

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

When dose reduction is necessary during the treatment of hepatocellular carcinoma (HCC) and advanced renal cell carcinoma (RCC), the NEXAVAR dose should be reduced to two tablets of 200 mg once daily (see Special warnings and precautions for use).

When dose reduction is necessary during the treatment of differentiated thyroid carcinoma, the NEXAVAR dose should be reduced to 600 mg 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-haematological adverse reactions, the dose of NEXAVAR may be increased.

Table 1. Suggested Dose Reduction Levels for Patients with Differentiated Thyroid Carcinoma

Dose Level	**Total daily dose**	Dosage
0	800 mg daily dose	(400 mg twice daily, 2 tablets twice daily)
-1	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)
-2	400 mg daily dose	(200 mg twice daily, 1 tablet twice daily)
-3	200 mg daily dose	(200 mg once daily, one tablet once daily)

Table 2. Suggested Dose Modifications for Skin Toxicity in Patients with Differentiated Thyroid Carcinoma

Grade	Occurrence	NEXAVAR dose modification*
Grade 1	Any	Institute supportive measures immediately and continue NEXAVAR treatment
Grade 2	First	Institute supportive measures immediately and consider a decrease NEXAVAR dose to 600 mg daily (400 mg and 200 mg 12 hours apart) If no improvement within 7 days, see below
	No improvement within 7 days or second occurrence	Interrupt NEXAVAR until resolved to grade 0-1. When NEXAVAR is resumed, decrease dose by one dose level
	Third	Interrupt NEXAVAR until resolved to grade 0-1. When NEXAVAR is resumed, decrease dose by two dose levels
	Fourth	Discontinue NEXAVAR permanently
Grade 3	First	Interrupt NEXAVAR until resolved to grade 0-1. When NEXAVAR is resumed, decrease dose by one dose level
	Second	Interrupt NEXAVAR until resolved to grade 0-1. When NEXAVAR is resumed, decrease dose by two dose levels
	Third	Discontinue NEXAVAR permanently

*For patients who require a dose reduction for Grade 2 or 3 skin toxicity, the dose of NEXAVAR may be increased if skin toxicity improved to Grade 0-1 after at least 28 days treatment on the reduced dose of NEXAVAR

Elderly (above 65 years), Gender and Body Weight

No dose adjustment is required on the basis of patient age (above 65 years), gender, or body weight.

Use in Patients with Renal Impairment

No dose adjustment is required in patients with mild to moderate renal impairment. NEXAVAR has not been studied in patients with severe renal impairment or patients undergoing dialysis (see Pharmacokinetic properties - Renal Impairment). Monitoring of fluid balance and electrolytes in patients at risk of renal dysfunction is advised.

Use in Patients with Hepatic Impairment

No dose adjustment is required in patients with Child-Pugh A or B hepatic impairment. NEXAVAR has not been studied in patients with Child-Pugh C hepatic impairment (see Pharmacokinetics - Hepatic Impairment).

Paediatric population

The safety and effectiveness of NEXAVAR in paediatric patients has not been established.

4.3 Contraindications

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

4.4 Special warnings and precautions for use

Pregnancy and Lactation

Women should avoid becoming pregnant while on therapy. Women of childbearing potential must be apprised of the potential hazard to the fetus, which includes severe malformation (teratogenicity), failure to thrive and fetal death (embryotoxicity) (see Use in Pregnancy and Lactation).

NEXAVAR should not be used during pregnancy. Breastfeeding should be discontinued during NEXAVAR therapy (see Use in Lactation).

Dermatological Toxicities

Hand-foot skin reaction (palmar-plantar erythrodysaesthesia) and rash represent the most common adverse medicine reactions with 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. As seen in one clinical study, the incidence of hand-foot skin reaction may be higher in the Asian population. 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 (see Undesirable effects).

Hypertension

An increased incidence of hypertension was observed in NEXAVAR-treated patients. Hypertension was usually mild to moderate, occurred early in the course of treatment, and was amenable to management with standard antihypertensive therapy. Blood pressure should be monitored regularly and treated, if required, in accordance with standard medical practice. In cases of severe or persistent

hypertension, or hypertensive crisis despite adequate antihypertensive therapy, permanent discontinuation of NEXAVAR should be considered (see Undesirable effects).

Aneurysms and artery dissections

The use of VEGF pathway inhibitors in patients with or without hypertension may promote the formation of aneurysms and/or artery dissections. Before initiating NEXAVAR, this risk should be carefully considered in patients with risk factors such as hypertension or history of aneurysm.

Haemorrhage

An increase in the risk of bleeding may occur following NEXAVAR administration. The incidence of severe bleeding events is uncommon. If any bleeding event necessitates medical intervention, it is recommended that permanent discontinuation of NEXAVAR should be considered (see Undesirable effects). Due to the potential risk of bleeding, tracheal, bronchial, and oesophageal infiltration should be treated with localised therapy prior to administering NEXAVAR in patients with differentiated thyroid carcinoma.

Tumour lysis syndrome

Cases of tumour lysis syndrome, some fatal, have been reported in post-marketing surveillance in patients treated with sorafenib. Risk factors for tumour lysis syndrome include high tumour burden, pre-existing chronic renal insufficiency, oliguria, dehydration, hypotension, and acidic urine. These patients should be monitored closely and treated promptly as clinically indicated, and prophylactic hydration should be considered.

Warfarin

Infrequent bleeding events or elevations in the International Normalised Ratio (INR) have been reported in some patients taking warfarin while on NEXAVAR therapy. Patients taking warfarin concomitantly should be monitored regularly for changes in prothrombin time, INR and for clinical bleeding episodes (see Undesirable effects).

Wound Healing Complications

No formal studies of the effect of NEXAVAR on wound healing have been conducted. In patients undergoing major surgical procedures, temporary interruption of NEXAVAR therapy is recommended for precautionary reasons. There is limited clinical experience regarding the timing of re-initiation of 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.

Cardiac Ischaemia and/or Infarction

In Study 11213, the incidence of treatment-emergent cardiac ischaemia/infarction events was higher in the NEXAVAR group (4.9%) compared with the placebo group (0.4%). In Study 100554, the incidence of treatment-emergent cardiac ischaemia/infarction events was 2.7% in sorafenib patients compared with 1.3% in the placebo group. Patients with unstable coronary artery disease or recent myocardial infarction were excluded from these studies. Temporary or permanent discontinuation of NEXAVAR should be considered in patients who develop cardiac ischaemia and/or infarction (see Undesirable effects).

QT Interval Prolongation

NEXAVAR has been shown to prolong the QT/QTc interval (see Pharmacodynamic properties), which may lead to an increased risk for ventricular arrhythmias. Use NEXAVAR 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 hypokalaemia, hypocalcaemia, or hypomagnesaemia. When using NEXAVAR in these patients, periodic monitoring with on-treatment electrocardiograms and electrolytes (magnesium, potassium, calcium) should be considered.

Gastrointestinal Perforation

Gastrointestinal perforation is an uncommon event and has been reported in less than 1% of patients taking NEXAVAR. In some cases, this was not associated with apparent intra-abdominal tumour. NEXAVAR therapy should be discontinued if gastrointestinal perforation develops.

Hepatic Impairment

Experience in Child-Pugh B hepatic impairment is limited. No data is available on patients with Child-Pugh C (severe) hepatic impairment. Since sorafenib is mainly eliminated via the hepatic route, exposure might be increased in patients with severe hepatic impairment (see Pharmacokinetic properties).

Drug-induced Hepatitis

Drug-induced hepatitis has been observed in post-marketing experience. Sorafenib should be discontinued if drug-induced hepatitis is suspected.

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).

TSH Suppression in Differentiated Thyroid Carcinoma (DTC)

In the DTC clinical trials, increases in TSH levels above 0.5mU/L were observed in NEXAVAR treated patients. When using NEXAVAR in differentiated thyroid carcinoma patients, close monitoring of TSH level is recommended.

Paediatric Use

The safety and effectiveness of NEXAVAR in paediatric patients has not been established.

Effects on bone and teeth were observed after repeated dosing to young and growing dogs. The changes consisted of irregular thickening of the femoral growth plate at a dose of 30 mg/kg/day (relative exposure 0.5 based on relative AUC for unbound drug), hypocellularity of the bone marrow at 10 mg/kg/day (relative exposure, 0.25) and alteration of dentin composition at 30 mg/kg/day (relative exposure, 0.3). Similar effects were observed in mice and rats. A study in adult dogs revealed no effects on teeth and minimal effects on bone marrow.

4.5 Interaction with other medicines and other forms of interaction

Sorafenib is metabolized primarily in the liver undergoing oxidative metabolism, mediated by CYP3A4, as well as glucuronidation mediated by UGT1A9. Studies with human liver microsomes demonstrated that sorafenib is a competitive inhibitor of CYP2B6, CYP2C8, and CYP2C9 (Ki =1-8 μM).

Caution is recommended when administering NEXAVAR together with compounds that are metabolised / eliminated predominantly by the UGT1A1 pathway (e.g. irinotecan). *In vitro* data show that sorafenib inhibits glucuronidation by the UGT1A1 (Ki = 1μM) and UGT1A9 (Ki = 2μM) pathways. Concomitant clinical administration of sorafenib 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 be increased when co-administered with sorafenib.

CYP inducers

CYP1A2 and CYP3A4 activities were not altered after treatment of cultured human hepatocytes with sorafenib, indicating that sorafenib is unlikely to be an inducer of CYP1A2 and CYP3A4. 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 metabolism of NEXAVAR and thus decrease NEXAVAR concentrations.

CYP3A4 Inhibitors

Ketoconazole (400 mg), a potent inhibitor of CYP3A4, administered once daily for 7 days to healthy male volunteers did not alter the mean AUC of a single 50 mg dose of NEXAVAR. Therefore, clinical pharmacokinetic interactions of NEXAVAR with CYP3A4 inhibitors are unlikely.

CYP2C9 Substrates

In vitro 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 warfarin, a CYP2C9 substrate, was assessed *in vivo* in NEXAVAR-treated patients compared to placebo treated patients. The concomitant treatment with NEXAVAR and warfarin did not result in changes in mean PT-INR compared to placebo suggesting that NEXAVAR may not be an *in vivo* inhibitor of CYP2C9. However, patients taking warfarin should have their INR checked regularly.

CYP Isoform-selective Substrates

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

Sorafenib inhibits CYP2B6 and CYP2C8 *in vitro* with Ki values of 6 and 1–2 μM, respectively. Concomitant clinical administration of sorafenib with paclitaxel resulted in an increase, instead of a decrease, in the exposure of 6-OH paclitaxel, the active metabolite of paclitaxel that is formed by CYP2C8. These data suggest that sorafenib may not be an *in vivo* inhibitor of CYP2C8. Concomitant clinical administration of sorafenib with cyclophosphamide resulted in a small decrease in cyclophosphamide exposure, but no decrease in the systemic exposure of 4-OH cyclophosphamide, the active metabolite of cyclophosphamide that is formed primarily by CYP2B6. These data suggest that sorafenib may not be an *in vivo* inhibitor of CYP2B6.

Combination with other Anti-neoplastic Agents

In clinical studies, NEXAVAR 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. NEXAVAR had no clinically relevant effect on the pharmacokinetics of gemcitabine, cisplatin, carboplatin, oxaliplatin, or cyclophosphamide.

Paclitaxel/Carboplatin

Administration of paclitaxel (225 mg/m^2) and carboplatin (AUC = 6) with sorafenib (≤ 400 mg twice daily), administered with a 3-day break in sorafenib dosing around administration of paclitaxel/carboplatin, resulted in no significant effect on the pharmacokinetics of paclitaxel.

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

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

Capecitabine

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

Doxorubicin/Irinotecan

Concomitant treatment with NEXAVAR resulted in a 21% increase in the AUC of doxorubicin. When administered with irinotecan, whose active metabolite SN-38 is further metabolized by the UGT1A1 pathway, there was a 67-120% increase in the AUC of SN-38 and a 26-42% increase in the AUC of irinotecan. The clinical significance of these findings is unknown (see Special warnings and precautions for use).

Docetaxel

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

Combination with antibiotics

Neomycin

Co-administration of neomycin, a non-systemic antimicrobial agent used to eradicate GI flora, interferes with the enterohepatic recycling of sorafenib (see Pharmacokinetic properties - Metabolism

and Elimination), resulting in decreased sorafenib exposure. In healthy volunteers treated with a 5-day regimen of neomycin the average bioavailability of sorafenib decreased by 54%. The clinical significance of these findings is unknown. Effects of other antibiotics have not been studied, but will likely depend on their ability to decrease glucuronidase activity.

Combination with proton pump inhibitors

Omeprazole

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

4.6 Fertility, pregnancy and lactation

Use in Pregnancy

Pregnancy Category D

There are no adequate and well-controlled studies in pregnant women using NEXAVAR. Sorafenib has been shown to be embryotoxic and teratogenic when administered to rats and rabbits. Observed effects included decreases in maternal and fetal body weights, an increased number of fetal resorptions and an increased number of skeletal and visceral malformations. Adverse fetal outcomes were observed at an oral dose of 1 mg/kg/day in rats (relative exposure, 0.08) and 3 mg/kg/day in rabbits (relative exposure, 0.4). In rats, sorafenib and/or its metabolites were demonstrated to cross the placenta. NEXAVAR therapy in pregnant patients is anticipated to inhibit angiogenesis in the fetus.

NEXAVAR should not be used during pregnancy. Women must be advised to avoid becoming pregnant while on therapy. If NEXAVAR is used during pregnancy or if the patient becomes pregnant while using NEXAVAR, the patient must be apprised of the potential hazard to the fetus, which includes severe malformation (teratogenicity), failure to thrive and fetal death (embryotoxicity). Adequate contraception should be used during therapy and for at least 2 weeks after completion of therapy.

Use in Lactation

It is not known whether NEXAVAR is excreted in human milk. In lactating rats, sorafenib and/or its metabolites were readily excreted in milk (milk: plasma AUC ratio of approximately 5:1). Because of the potential for excretion in human milk and the likelihood that infants will be particularly sensitive to the toxic effects of sorafenib, women must be advised to discontinue breastfeeding during NEXAVAR treatment.

Effects on Fertility

No specific studies with NEXAVAR have been conducted in animals to evaluate the effect on fertility. An adverse effect on male and female fertility is expected, however, based on histological changes in reproductive organs observed in repeat-dose studies in animals. Sorafenib caused testicular tubular degeneration and oligospermia in mice, rats, and dogs at daily doses producing plasma exposures approximately 0.9, 1.5 and 0.3 times respectively that expected in patients (based on relative AUC for unbound sorafenib). Retardation of prostatic and seminal vesicle development was also observed in rats. In female mice and rats, arrested follicular development in the ovaries was observed following treatment with sorafenib at doses producing exposure levels 0.7 and 0.9 times respectively that expected in patients.

4.7 Effects on ability to drive and use machines

No studies on the effects of sorafenib on the ability to drive or use machines have been performed. There is no evidence that sorafenib affects the ability to drive or operate machinery.

4.8 Undesirable effects

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

Renal Cell Carcinoma

The overall safety profile of NEXAVAR is based on 1286 cancer patients, who received NEXAVAR as single agent.

Table 3 includes all medicine-related adverse events that are reported in at least 5% of patients in the TARGET Study (see Clinical efficacy and safety). The most common medicine-related adverse events reported with NEXAVAR were diarrhoea, fatigue, alopecia, infection, rash, and hand-foot skin reaction (corresponds to palmar plantar erythrodysaesthesia syndrome in MedDRA).

Table 3. Adverse reactions reported in at least 5% of patients in any treatment group – Study 11213 in renal cell carcinoma (see study 11213).

System Organ Class/ Preferred term	NEXAVAR N = 451			Placebo N = 451		
	All Grades %	Grade 3 %	Grade 4 %	All Grades %	Grade 3 %	Grade 4 %
Metabolism and Nutrition Disorders						
Anorexia	9	<1	0	5	<1	0
Nervous System Disorders						
Headache	6	0	0	3	0	0
Vascular Disorders						
Hypertension	12	2	<1	1	<1	0
Flushing	6	0	0	2	0	0
Gastrointestinal Disorders						
Diarrhoea	38	2	0	9	<1	0
Nausea	16	<1	0	12	<1	0
Vomiting	10	<1	0	6	<1	0
Constipation	6	0	0	3	0	0
Skin and Subcutaneous Tissue Disorders						
Rash	28	<1	0	9	<1	0
Alopecia	25	<1	0	3	0	0
Hand-foot skin reaction **	19	4	0	3	0	0
Pruritus	17	<1	0	4	0	0
Erythema	15	0	0	4	0	0
Dry skin	11	0	0	2	0	0
Skin exfoliation	7	<1	0	2	0	0
Musculoskeletal, Connective Tissue and Bone Disorders						
Pain in extremity	6	<1	0	2	0	0
Arthralgia	6	<1	0	3	0	0
General Disorders and Administration Site Conditions						
Fatigue	15	2	0	11	<1	0
Asthenia	9	<1	0	4	<1	0

** palmar plantar erythrodysaethesia syndrome in MedDRA

Hepatocellular Carcinoma

Table 4. Adverse reactions reported in at least 5% of patients in any treatment group – Study 100554 in hepatocellular carcinoma (see study 100554).

System organ class/ Preferred term	Nexavar N = 297			Placebo N = 302		
	All Grades %	Grade 3 %	Grade 4 %	All Grades %	Grade 3 %	Grade 4 %
Metabolism and Nutrition Disorders						
Anorexia	11	<1	0	3	<1	0
Gastrointestinal Disorders						
Diarrhea	39	8	0	11	2	0
Nausea	11	<1	0	8	1	0
abdominal pain	7	2	0	3	<1	0
Vomiting	5	1	0	3	<1	0
Skin and Subcutaneous Tissue Disorders						
Hand-foot skin reaction **	18	7	0	2	0	0
alopecia	14	0	0	2	0	0
Rash	11	<1	0	8	0	0
pruritus	8	0	0	7	<1	0
dry skin	8	0	0	4	0	0
General Disorders and Administration Site conditions						
fatigue	17	2	<1	13	3	<1
asthenia	6	1	<1	2	<1	0
Investigations						
weight decreased	9	2	0	<1	0	0
Respiratory, thoracic and mediastinal disorders						
hoarseness	5	0	0	<1	0	0

** palmar plantar erythrodysaethesia syndrome in MedDRA

Differentiated thyroid carcinoma

Adverse Reactions in Differentiated Thyroid Carcinoma study 14295: double blind period

Table 5 shows the percentage of differentiated thyroid carcinoma patients experiencing adverse reactions (TEAE – treatment emergency adverse events) that were reported in at least 5% of patients and at a higher rate in the NEXAVAR treated subjects than the placebo arm in double blind phase. CTCAE Grade 3 adverse reactions were reported in 53% of patients receiving NEXAVAR compared to 23% of patients receiving placebo. CTCAE Grade 4 adverse reactions were reported in 12% of patients receiving NEXAVAR compared to 7% of patients receiving placebo.

Table 5. Adverse reactions reported in at least 5% of patients treated with NEXAVAR and more commonly than in patients receiving placebo – Study 14295 in differentiated thyroid carcinoma (double blind period, safety analysis set) - see Clinical efficacy and safety

System Organ Class/ Preferred term	NEXAVAR N = 207			Placebo N = 209		
	All Grades %	Grade 3 %	Grade 4 %	All Grades %	Grade 3 %	Grade 4 %
Metabolism and Nutrition Disorders						
anorexia	30.4	1.9	0	4.8	0	0
hypocalcaemia	16.4	5.8	2.9	4.8	<1	1.0
hypokalaemia	6.8	1.4	0	2.4	0	0
Nervous System Disorders						
headache	16.9	0	0	6.2	0	0
paraesthesia	7.2	<1	0	2.9	0	0
dizziness	6.3	0	0	2.4	0	0
dysgeusia	5.8	0	0	0	0	0
Vascular Disorders						
hypertension	38.2	9.2	0	11.0	1.9	0
Gastrointestinal Disorders						
diarrhoea	67.6	5.3	<1	14.8	1.0	0
nausea	20.8	0	0	11.5	0	0
constipation	15.5	0	0	7.7	<1	0
vomiting	11.1	<1	0	5.7	0	0
stomatitis	11.1	<1	0	2.4	0	0
abdominal pain	10.6	1.0	0	2.9	<1	0
abdominal pain upper	8.7	<1	0	3.8	<1	0
dry mouth	7.7	0	0	3.8	0	0
dyspepsia	5.3	0	0	4.3	0	0
dysphagia	5.3	1.4	0	2.9	1.0	0
Skin and Subcutaneous Tissue Disorders						
Hand-foot skin reaction **	69.1	19.3	0	7.7	0	0
alopecia	66.7	0	0	7.7	0	0
rash	35.3	4.8	0	7.2	0	0
pruritis	20.3	<1	0	10.5	0	0
dry skin	13.0	<1	0	4.8	0	0
erythema	10.1	0	0	<1	0	0
hyperkeratosis	7.2	0	0	0	0	0

System Organ Class/ Preferred term	NEXAVAR N = 207			Placebo N = 209		
	All Grades %	Grade 3 %	Grade 4 %	All Grades %	Grade 3 %	Grade 4 %
Respiratory, thoracic and mediastinal dosorders						
cough	15.0	0	0	13.9	0	0
dysphonia	12.6	<1	0	3.3	0	0
dyspnoea	12.1	4.3	0	10.5	2.4	1.0
oropharyngeal pain	9.2	0	0	2.9	0	0
epistaxis	7.2	0	0	1.0	0	0
Musculoskeletal, Connective Tissue and Bone Disorders						
pain in extremity	14.5	1.0	0	6.7	0	0
arthralgia	10.1	0	0	7.7	1.4	0
muscle spasms	10.1	0	0	2.9	0	0
Blood and lymphatic system disorders						
anaemia	5.3	1.0	0	3.8	<1	0
General Disorders and Administration Site Conditions						
fatigue	41.1	4.8	0	20.1	1.0	0
asthenia	12.1	0	0	6.7	0	0
pyrexia	10.6	1.0	0	4.8	0	0
mucosal inflammation	10.1	1.0	<1	<1	0	0
chest pain	8.2	0	0	2.9	0	0
nasopharyngitis	6.8	0	0	5.3	0	0
urinary tract infection	5.3	0	0	2.4	0	0
Investigations						
weight decreased	48.8	5.8	0	13.9	1.0	0
blood thyroid stimulating hormone increased*	33.3	0	0	13.4	0	0
alanine aminotransferase increased	12.6	2.4	<1	4.3	0	0
aspartate aminotransferase increased	11.1	1.0	0	2.4	0	0

* blood TSH increased was collected as an AE when TSH was >0.5 mU, as this was the target for TSH suppression in this study

** palmar plantar erythrodysaesthesia syndrome in MedDRA

Multiple Clinical Trials

Medicine related adverse reactions reported in multiple clinical trials or have been identified through post marketing use are listed below in Table 6, by system organ class (in MedDRA) and frequency. Frequencies are defined as: very common (≥ 10%), common (≥ 1% to < 10%), uncommon (≥ 0.1% to < 1%), rare (≥ 0.01% to < 0.1%). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Table 6. All Adverse Medicine Reactions reported in patients in multiple clinical trials in MedDRA Coding

System Organ Class	Very Common ≥10%	Common ≥1% to <10%	Uncommon ≥0.1% to <1%	Rare ≥0.01% to <0.1%
Infections and Infestations	infection	folliculitis		
Blood and Lymphatic System Disorders	lymphopaenia	leucopaenia neutropaenia anaemia thrombocytopaenia		
Immune system Disorders			anaphylactic reaction hypersensitivity reactions (including skin reactions and urticaria)	
Endocrine Disorders		hypothyroidism	hyperthyroidism	
Metabolism and Nutrition Disorders	anorexia hypophosphataemia	hypocalcaemia hypokalemia hyponatraemia	dehydration	
Psychiatric Disorders		depression		
Nervous System Disorders		peripheral sensory neuropathy dysgeusia	reversible posterior leukoencephalopathy*	
Ear and Labyrinth Disorders		tinnitus		
Cardiac Disorders		congestive heart failure* myocardial ischaemia and/or infarction*		QT prolongation
Vascular Disorders	haemorrhage (inc. gastrointestinal* respiratory tract* and cerebral haemorrhage*) hypertension	flushing	hypertensive crisis*	
Respiratory, Thoracic and Mediastinal Disorders		rhinorrhoea dysphonia	interstitial lung disease-like events* (includes reports of pneumonitis, radiation pneumonitis, acute respiratory distress, interstitial pneumonia, pulmonitis and lung inflammation)	

System Organ Class	Very Common ≥10%	Common ≥1% to <10%	Uncommon ≥0.1% to <1%	Rare ≥0.01% to <0.1%
Gastrointestinal Disorders	diarrhoea nausea vomiting constipation	stomatitis (including dry mouth and glossodynia) dyspepsia dysphagia gastrooesophageal 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	keratoacanthomas/ squamous cell cancer of the skin dermatitis exfoliative acne skin desquamation hyperkeratosis	eczema erythema multiforme	
Musculoskeletal, Connective Tissue and Bone Disorders	arthralgia	myalgia muscle spasms		
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	weight decreased increased amylase increased lipase	transient increase in transaminases	transient increase in blood alkaline phosphatase INR abnormal, prothrombin level abnormal	

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

** palmar plantar erythrodysaesthesia syndrome in MedDRA

Post-marketing experience

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

Skin and subcutaneous tissue disorders: radiation recall dermatitis, Stevens-Johnson syndrome, leukocytoclastic vasculitis, toxic epidermal necrolysis

Immune system disorders: angioedema

Musculoskeletal, Connective Tissue and Bone Disorders: rhabdomyolysis

Vascular disorders: cases of aneurysms and artery dissections, sometimes fatal, have been reported with VEGFR pathway inhibitors.

Metabolism and nutrition disorders: tumour lysis syndrome

Further information on selected adverse drug reactions

Congestive Heart Failure

In company sponsored clinical trials, congestive heart failure was reported as an adverse event in 1.9% of patients treated with sorafenib (N = 2276). In study 11213 (RCC) adverse events consistent with congestive heart failure were reported in 1.7% of those treated with sorafenib and 0.7% receiving placebo. In study 100554 (HCC), 0.99% of those treated with sorafenib and 1.1% receiving placebo were reported with these events consistent with congestive heart failure.

Two randomised 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 treatment for patients with advanced Non-Small Cell Lung Cancer (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.

Additional information on special populations

In clinical trials, certain adverse drug reactions such as hand-foot skin reaction, diarrhoea, 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.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://nzphvc.otago.ac.nz/reporting/

4.9 Overdose

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 diarrhoea and dermatological events.

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

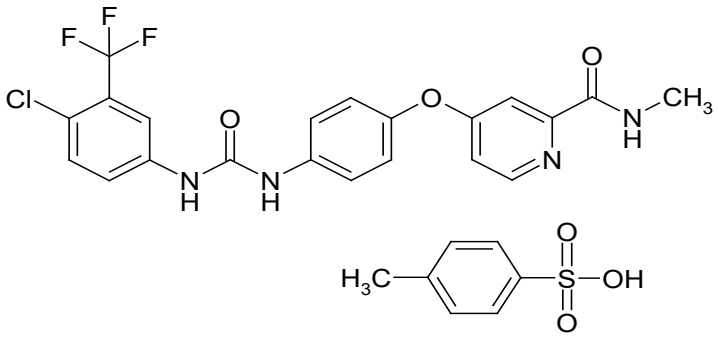
For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Sorafenib tosilate is 4-(4-{3-[4-Chloro-3-(trifluoromethyl)phenyl]-ureido}phenoxy)-N2-methylpyridine-2-carboxamide 4-methylbenzenesulfonate. The empirical formula is $C_{21}H_{16}ClF_3N_4O_3$ x $C_7H_8O_3S$ and the CAS number is 28844-1-73-01 (sorafenib) and 475207-59-1 (sorafenib tosilate).

Sorafenib tosilate has the following structural formula:



Sorafenib tosilate is a white to yellowish or brownish solid with a molecular weight of 637 g/mol. Sorafenib tosilate is practically insoluble in aqueous media, slightly soluble in ethanol and soluble in PEG 400.

Sorafenib is a multikinase inhibitor that targets various receptor tyrosine kinases and RAF kinases (serine/threonine kinases) associated with tumour growth. Sorafenib inhibits the activity of targets present in tumour cells [Raf-1 (CRAF), BRAF, V600E BRAF, KIT and FLT-3] and in the tumour vasculature [Raf-1 (CRAF), VEGFR-2, VEGFR-3 and PDGFR-β]. Sorafenib has been shown to inhibit tumour cell proliferation *in vitro*, and to inhibit the growth of mouse renal cell carcinoma (RENCA) allografts, human renal cell carcinoma (A498) xenografts, and differentiated thyroid carcinoma, as well as a broad range of other human tumour xenografts, in nude mice. Inhibition of tumour growth was accompanied by a reduction in tumour angiogenesis.

Clinical efficacy and safety

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

Hepatocellular Carcinoma

Study 100554 was a Phase III, international, multi-centre, randomised, double blind, placebo-controlled trial in 602 patients with hepatocellular carcinoma. Overall survival (OS) was a primary endpoint of this study, time to progression (TTP) a secondary endpoint.

Demographics and baseline disease characteristics were comparable between the NEXAVAR and placebo groups with regard to age, gender, race, performance status, aetiology (including hepatitis B, hepatitis C and alcoholic liver disease), TNM (tumour node metastasis) 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 tumour spread (30.1% vs. 30.0%), and BCLC (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 function Child-Pugh status was comparable between the NEXAVAR and placebo groups (A: 95% vs. 98%; B: 5% vs. 2%). Only one patient with Child-Pugh C liver dysfunction was treated in the study. Prior treatment included surgical resection procedures (19.1% vs. 20.5%), locoregional therapies (including radiofrequency ablation, percutaneous ethanol injection and transarterial chemoembolisation; 38.8% vs. 40.6%), radiotherapy (4.3% vs. 5.0%) and systemic therapy (3.0% vs. 5.0%).

The study was stopped after a planned interim analysis of OS had crossed the prespecified efficacy boundary. This OS analysis showed a statistically significant advantage for NEXAVAR over placebo for OS (HR: 0.69; p = 0.00058, see Table 7 and Figure 1). This advantage was consistent across all subsets analysed. In the prespecified stratification factors [ECOG (Eastern Cooperative Oncology Group) status, presence or absence of macroscopic vascular invasion and/or extrahepatic tumour spread, and region] the hazard ratio consistently favoured NEXAVAR over placebo. The TTP (by independent radiological review) was significantly longer in the NEXAVAR arm (HR: 0.58; p = 0.000007, see Table 7).

Table 7. Efficacy Results from Study 100554 in hepatocellular carcinoma

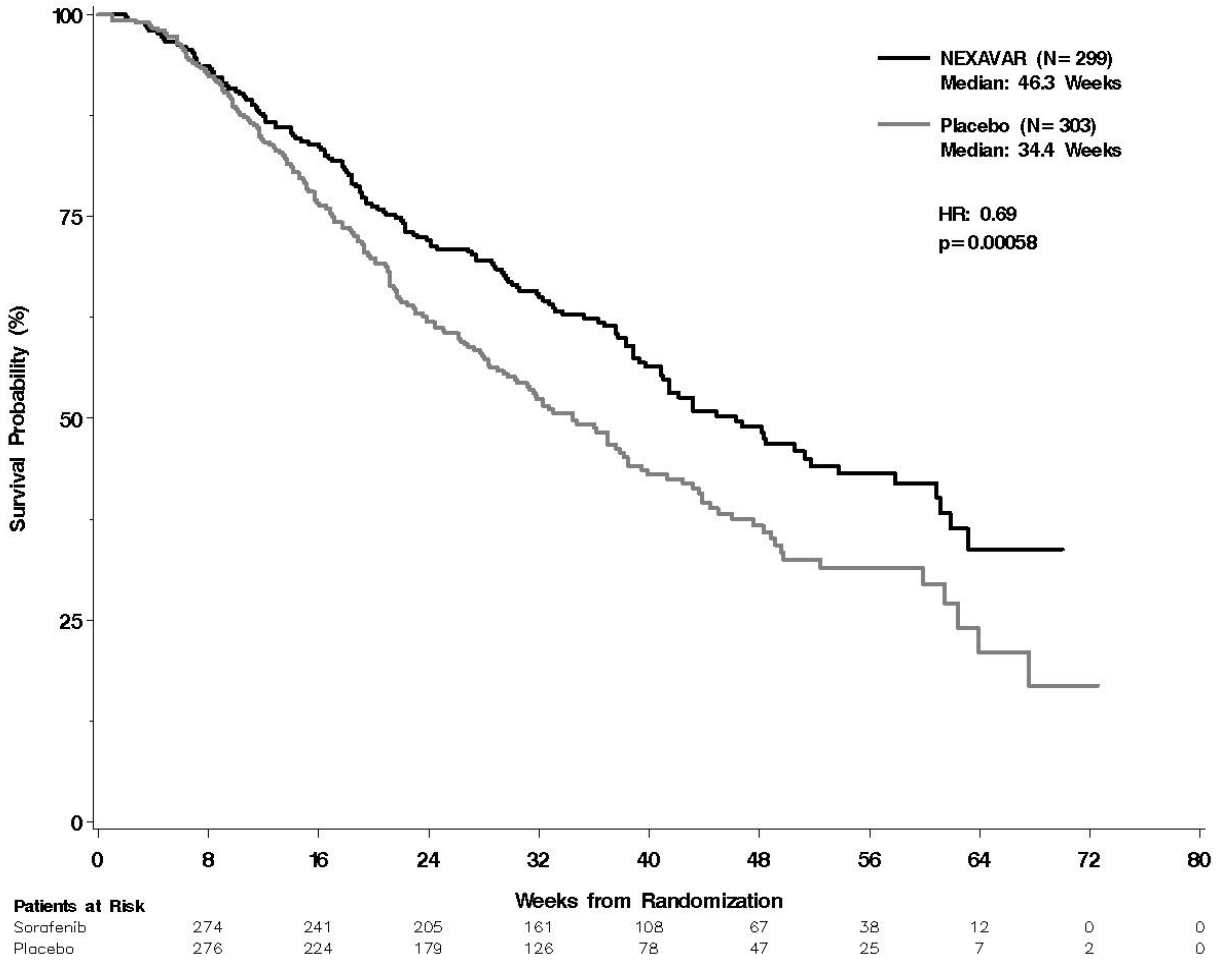
Efficacy Parameter	**Nexavar (N = 299)**	**Placebo (N = 303)**	**P-value**	**HR (95% CI)**
Overall Survival (OS) [median, months (95% CI)]	10.7 (9.4, 13.3)	7.9 (6.8, 9.1)	0.00058*	0.69 (0.55, 0.87)
Time to Progression (TTP) [median, months (95% CI)]**	5.5 (4.1, 6.9)	2.8 (2.7, 3.9)	0.000007	0.58 (0.45, 0.74)

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

* statistically significant because the p-value was below the prespecified O'Brien Fleming stopping boundary of 0.0077

** independent radiological review

Figure 1: Kaplan-Meier curve of overall survival in Study 100554, intent-to-treat population)



The rate of complete or partial response observed in either investigator assessment or independent radiological review was low, and there was little difference between the NEXAVAR and placebo arms (Table 8 and Table 9). However, the disease control rate (DCR), a different measure of clinical benefit assessing sustained disease stabilization in patients for at least 28 days, was superior in the NEXAVAR arm, with 43.48% of patients achieving disease control, compared to 31.68% in the placebo arm.

Table 8. Overall best tumour response by independent radiological review (ITT analysis)

Best Response*	**Nexavar (N = 299) n (%)**	**Placebo (N = 303) n (%)**
Complete Response (CR)	0	0
Partial Response (PR)	7 (2.34)	2 (0.66)
Stable Disease	211 (70.57)	204 (67.33)
Progressive Disease (PD)	54 (18.06)	73 (24.09)
Not assessable	27 (9.03)	24 (7.92)
Disease Control Rate (DCR)	130 (43.48)	96 (31.68)

* determined according to RECIST (Response Evaluation Criteria in Solid Tumours)

Table 9. Overall best tumour response by investigator assessment (ITT analysis)

Best Response*	**Nexavar (N = 299) n (%)**	**Placebo (N = 303) n (%)**
Complete Response (CR)	0 (0.00)	0 (0.00)
Partial Response (PR)	18 (6.02)	8 (2.64)
Stable Disease	181 (60.54)	167 (55.12)
Progressive Disease (PD)	77 (25.75)	101 (33.33)
Not assessable	23 (7.69)	27 (8.91)

* determined according to RECIST (Response Evaluation Criteria in Solid Tumours)

Renal Cell Carcinoma

Study 11213, TARGET (Treatment Approaches in Renal cancer Global Evaluation Trial)

The TARGET study was a Phase III multi-centre, randomised, double blind, placebo-controlled trial in 903 patients with advanced renal cell carcinoma who had received prior systemic therapy. Primary study end points included overall survival and progression free survival (PFS). Tumour response rate was a secondary endpoint.

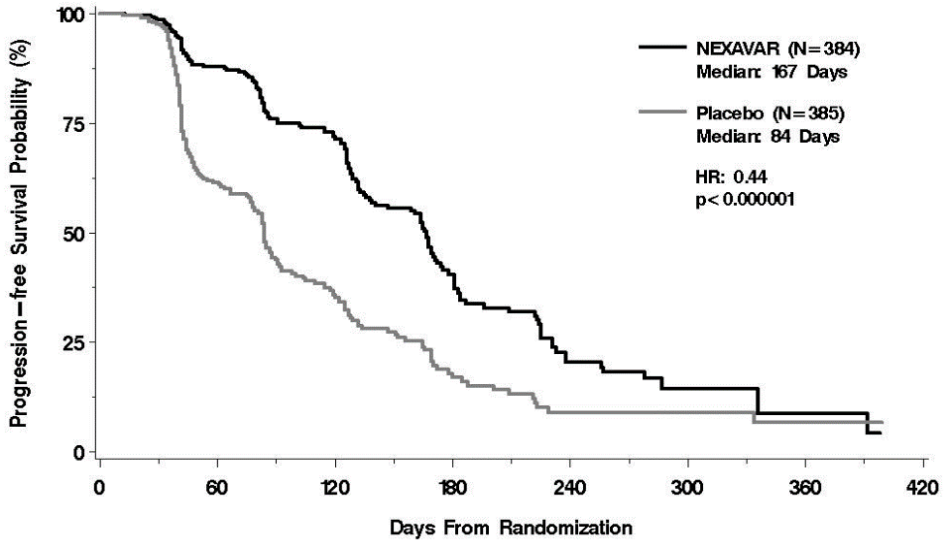
Patients were randomised to NEXAVAR 400 mg twice daily (N = 451) or to placebo (N = 452). Baseline demographics and patient characteristics were well balanced for both treatment groups. Approximately half of the patients had an ECOG performance status of 0 and half of the patients were in the low MSKCC (Memorial Sloan Kettering Cancer Centre) prognostic group.

Two planned interim analyses of survival were conducted. In the first analysis based on 220 deaths, the estimated hazard ratio (risk of death with NEXAVAR compared to placebo) was 0.72 (95% CI: 0.55-0.95; p = 0.018. The threshold for statistical significance of the interim analysis was p < 0.0005). As of 30 November 2005, 367 deaths were reported, comprising 68% of the protocol-specified 540 survival events, there was an estimated 30% improvement in overall survival for patients receiving NEXAVAR compared to placebo. A total of 216 placebo patients had crossed over to NEXAVAR treatment. The median overall survival for the NEXAVAR and placebo group was 19.3 months and 15.9 months, respectively. The estimated hazard ratio (risk of death with sorafenib compared to placebo) was 0.77 (95% CI: 0.63-0.95; p = 0.015. The threshold for statistical significance of the interim analysis was p < 0.0094).

Progression free survival in the intent-to-treat population was evaluated by blinded independent radiological review using RECIST criteria. Figure 2 depicts Kaplan-Meier curves for PFS. The PFS analysis was a two-sided Log-Rank test stratified by Motzer/MSKCC prognostic risk category[1] and country.

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

Figure 2: Kaplan-Meier Curves for Progression Free Survival

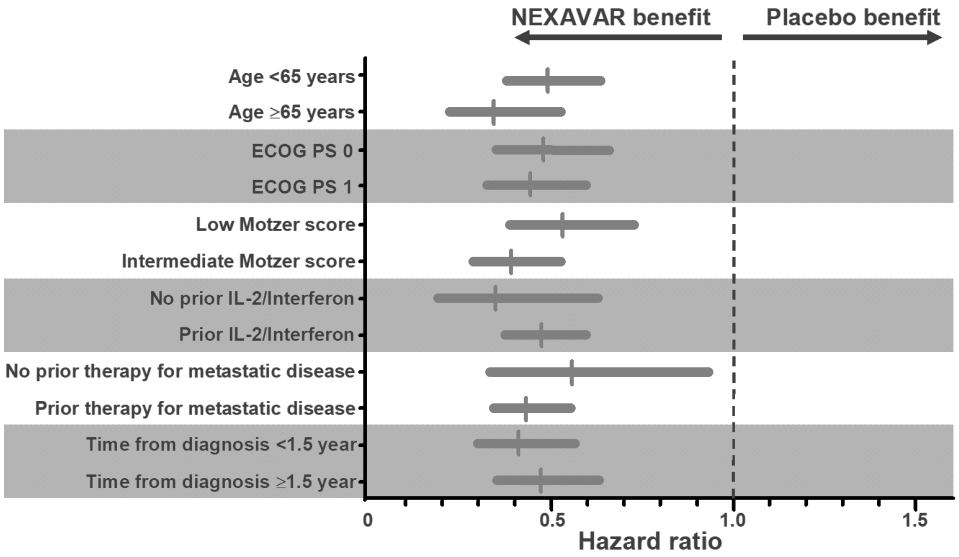


NOTE: HR is from Cox regression model with the following covariates: Motzer/MSKCC prognostic risk category[1] and country. P-value is from two-sided Log-Rank test stratified by Motzer/MSKCC prognostic risk category[1] and country.

The PFS analysis included 769 patients randomised to NEXAVAR 400 mg twice daily (N = 384) or to placebo (N = 385). The median progression free survival was double for patients randomised to NEXAVAR (167 days) compared to patients randomised to placebo (84 days), (HR: 0.44; 95% CI: 0.35-0.55; p < 0.000001).

A series of patient subsets were examined in exploratory univariate analyses of PFS. These results are shown in Figure 3. The effect of NEXAVAR on PFS was consistent across these subsets, including patients with no prior IL-2 or Interferon therapy (N = 137), for whom the median PFS was 172 days on NEXAVAR compared to 85 days on placebo.

Figure 3: Progression Free Survival in Patient Subgroups (Hazard Ratio and 95% Cl for NEXAVAR : Placebo)



Best overall tumour response was determined by investigator radiological review according to RECIST criteria. In the NEXAVAR group 1 patient (0.2%) had a complete response, 43 patients (9.5%) had a partial response, and 333 patients (73.8%) had stable disease. In the placebo group 0 patients (0%)

had a complete response, 8 patients (1.8%) had a partial response, and 239 patients (52.9%) had stable disease.

In Study 11213, there were 41 deaths within 30 days of study medicine: 18 in the placebo group and 23 in the sorafenib group. Only 4 of the deaths in the sorafenib group occurred during treatment. The cause of death was reported as progression of RCC in 12 placebo patients and 18 sorafenib patients. The study was designed so that all patients were eligible for unblinding on progressive disease (PD), and those on the sorafenib arm were eligible to continue sorafenib treatment beyond documentation of PD per investigator discretion. Four of 23 deaths in the sorafenib group occurred after documented PD and continued open label sorafenib treatment. Furthermore, the mean duration of therapy in Study 11213 was 135.8 days for the sorafenib group and 93.8 days for the placebo group.

NEXAVAR demonstrated no overall deterioration in kidney-cancer specific symptoms (FKSI-10) or health-related quality of life compared to placebo.

Study 100391

Study 100391 was a Phase II discontinuation trial in patients with metastatic malignancies including RCC. The primary endpoint was percentage of randomised patients (N = 65) remaining progression-free at 24 weeks. Progression free survival was significantly longer in the NEXAVAR group (163 days) than in the placebo group (41 days) (p = 0.0001; HR: 0.29). The progression free rate was significantly higher in patients randomised to NEXAVAR (50%) than in the placebo patients (18%) (p = 0.0077).

Differentiated thyroid carcinoma

Study 14295, a Phase III, international, multi-centre, randomised, double blind, placebo-controlled trial included 417 patients with locally advanced or metastatic differentiated thyroid carcinoma refractory to radioactive iodine.

Progression-free survival (PFS) was the primary endpoint of the study. Secondary endpoints included overall survival (OS), tumour response rate and duration of response. Following progression, patients were allowed to receive open label NEXAVAR. Concomitant radioactive iodine treatment was not permitted.

Patients were included in the study if they experienced progression within 14 months of enrollment and had differentiated thyroid carcinoma (DTC) refractory to radioactive iodine (RAI). DTC refractory to RAI was defined as having a lesion without iodine uptake on a radioactive iodine (RAI) scan, or receiving cumulative RAI ≥ 600 mCi, or experiencing progression after a RAI treatment within 16 months of enrollment or after two RAI treatments within 16 months of each other.

Baseline demographics and patient characteristics were well balanced for both treatment groups. Metastases were present in the lungs in 86%, lymph node in 51% and bone in 27% of the patients. Almost all patients had thyroidectomy (99.5%) and had a median delivered cumulative radioactive activity of approximately 400 mCi. The majority of patients had papillary carcinoma (56.8%), followed by follicular (25.4%) and poorly differentiated carcinoma (9.6%).

The full analysis set included 207 patients randomised to NEXAVAR 400 mg twice daily and 210 patients randomised to placebo. PFS was evaluated by blinded independent radiological review using RECIST criteria.

Median PFS was 329 days (10.8 months) in the NEXAVAR group compared to 175 days (5.8 months) in the placebo group. (HR): 0.587; 95% Confidence Interval (CI): 0.454-0.758; one-sided p <0.0001). (Table 10, Figure 4)

The effect of NEXAVAR on PFS was consistent across all subsets including geographic region, age above or below 60 years, gender, histological subtype, tumour burden and presence or absence of bone metastasis.

There was no statistical difference in overall survival between the treatment groups (the HR was 0.802; 95% CI: 0.539- 1.194; one-sided p value of 0.138, Table 10). The median OS was not reached for either arm. One hundred fifty (71.4%) patients randomised to placebo and 55 (26.6%) patients randomised to NEXAVAR received open-label NEXAVAR.

The median duration of therapy in the double-blind period was 46 weeks (range 0.3-135) for patients receiving NEXAVAR and 28 weeks (range 1.7–132) for patients receiving placebo.

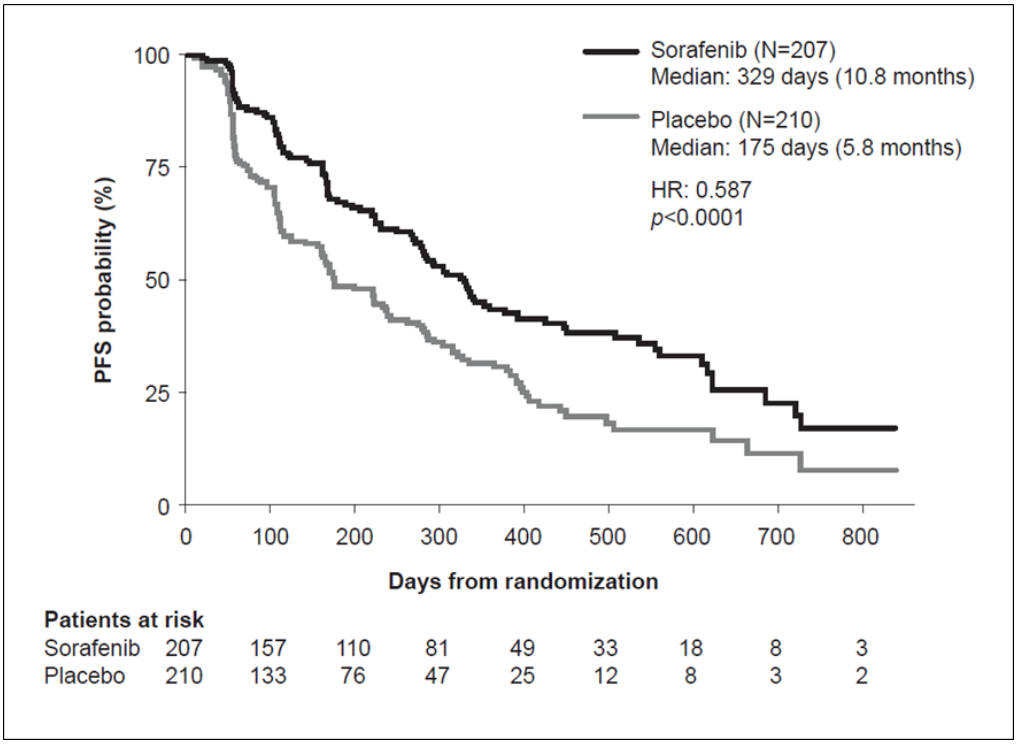
No complete response (CR) according to RECIST was observed. The overall response rate (CR + partial response (PR) per independent radiological assessment was higher in the NEXAVAR group (24 patients, 11.6%) than in the placebo group (1 patient, 0.5%), one-sided p<0.0001. The median duration of response was 309 days (95% CI: 226- 505 days) in NEXAVAR treated patients who experienced a PR.

Table 10. Efficacy Results from Study 14295 in Differentiated Thyroid Carcinoma

Efficacy Parameter	NEXAVAR (N=207)	Placebo (N=210)	P-value	HR (95% CI)
Progression-Free Survival (PFS) [median, days (95% CI)]*	329 (278, 393)	175 160, 238)	<0.0001	0.587 (0.454-0.758)
Overall Survival (OS) [median, days (95% CI)]	NR	NR	0.1381	0.802 (0.539-1.194)

NR = Not reached, CI=Confidence interval, HR=Hazard ratio (NEXAVAR over placebo)
*independent radiological review

Figure 4: Kaplan-Meier curve of Progression-Free Survival (PFS) in Study 14295 Thyroid carcinoma (full analysis set)



5.2 Pharmacokinetic properties

After administration of NEXAVAR tablets, the mean relative bioavailability is 38-49% when compared to an oral solution. Absolute bioavailability has not been determined.

The elimination half-life of sorafenib is approximately 25-48 hours. Multiple dosing of NEXAVAR for 7 days results in a 3 to 7-fold accumulation compared to single dose administration.

Steady state plasma sorafenib concentrations are achieved within 7 days, with a peak to trough ratio of mean concentrations of less than 2.

The steady-state pharmacokinetics of sorafenib administered at 400 mg twice a day were evaluated in thyroid carcinoma, renal cell carcinoma and hepatocellular carcinoma. The highest mean exposure was observed in thyroid carcinoma patients, though variability in exposure was high for all tumour types. The clinical relevance of the increased AUC in thyroid carcinoma patients is unknown.

Absorption and Distribution

Following oral administration, sorafenib reaches peak plasma levels in approximately 3 hours. When given with a moderate-fat meal, bioavailability is similar to that in the fasted state. With a high-fat meal, sorafenib bioavailability is reduced by 29% compared to administration in the fasted state.

Mean C_{max} and AUC increase 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 metabolised primarily in the liver undergoing oxidative metabolism, mediated by CYP3A4, as well as glucuronidation mediated by UGT1A9. Sorafenib conjugates may be cleaved in the GI tract by bacterial glucuronidase activity, allowing reabsorption of unconjugated drug. Co-administration of neomycin interferes with this process, decreasing the mean bioavailability of sorafenib by 54%.

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

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 faeces, and 19% of the dose excreted in urine as glucuronidated metabolites. Unchanged sorafenib, accounting for 51% of the dose, was found in faeces but not in urine.

Renal Impairment

In patients with normal renal function (N = 71) and in patients with mild renal impairment (CrCl > 50-80 mL/min, N = 24) or moderate renal impairment (CrCl 30-50 mL/min, N = 4), there was no relationship observed between steady state sorafenib AUC and renal function at doses of 400 mg twice daily. The pharmacokinetics of sorafenib has not been studied in patients with severe renal impairment (CrCl < 30 mL/min) or patients undergoing dialysis.

Hepatic Impairment

Sorafenib is cleared primarily by the liver.

In HCC patients with mild (Child-Pugh A) or moderate (Child-Pugh B) hepatic impairment, exposure values were within the range observed in patients without hepatic impairment. In non-HCC patients the pharmacokinetics (PK) of sorafenib in Child-Pugh A and Child-Pugh B patients were similar to the PK in healthy volunteers. The pharmacokinetics of sorafenib has not been studied in patients with severe (Child-Pugh C) hepatic impairment (see Special warnings and precautions for use).

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 ms and QTcF by 9±18 ms, as compared to placebo treatment at baseline. No subject showed a QTcB or QTcF >500 ms during the post-treatment ECG monitoring. (See Special warnings and precautions for use)

5.3 Preclinical safety data

Carcinogenicity

Carcinogenicity studies have not been performed with sorafenib.

Genotoxicity

Sorafenib has been tested for genotoxicity in a series of *in vitro* (bacterial mutation and mammalian chromosomal aberration) and *in vivo* (mouse micronucleus test) assays. Sorafenib did not cause genetic damage in the bacterial reverse mutation and mouse micronucleus tests. Weak clastogenicity was displayed by sorafenib in the *in vitro* mammalian chromosomal aberration assay (using Chinese Hamster lung cells) in the presence of metabolic activation but only at cytotoxic concentrations. An impurity in the final medicine (< 0.15%), picolinamide phenylether (PAPE), was mutagenic in the bacterial reverse mutation assay.

Effect on Laboratory Tests

Laboratory test abnormalities in RCC patients (study 11213)

Elevated lipase and amylase levels were very commonly reported. In the TARGET Study CTCAE grade 3 or 4 lipase elevations occurred in 10% of patients in the NEXAVAR group compared to 5% of patients in the placebo group. CTCAE grade 3 or 4 amylase elevations were reported in 1% of patients in the NEXAVAR group compared to 3% of patients in the placebo group. Clinical pancreatitis was reported in 2 of 384 NEXAVAR treated patients (CTCAE grade 4) and 1 of 384 patients (CTCAE grade 2) in the placebo group.

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

Laboratory abnormalities in HCC patients (study 100554)

Elevated lipase was observed in 40% of patients treated with NEXAVAR compared to 37% of patients in the placebo group. CTCAE Grade 3 or 4 lipase elevations occurred in 9% of patients in each group. Elevated amylase was observed in 34% of patients treated with NEXAVAR compared to 29% of patients in the placebo group. CTCAE Grade 3 or 4 amylase elevations were reported in 2% of patients in each group. Many of the lipase and amylase elevations were transient, and in the majority of cases

NEXAVAR treatment was not interrupted. Clinical pancreatitis was reported in 1 of 297 NEXAVAR-treated patients (CTCAE Grade 2).

Laboratory test abnormalities in thyroid carcinoma patients (study 14295)

Hypocalcaemia was reported in 35.7% of sorafenib treated patients compared to 11.0% of the patients in the placebo group. Most reports of hypocalcaemia were low grade. CTCAE grade 3 hypocalcaemia occurred in 6.8% of sorafenib treated patients and 1.9% of patients in the placebo group, and CTCAE grade 4 hypocalcaemia occurred in 3.4% of sorafenib treated patients and 1.0% of patients in the placebo group.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

In addition to sorafenib tosilate, each NEXAVAR tablet contains the following inactive ingredients: croscarmellose sodium, microcrystalline cellulose, hypromellose, sodium lauryl sulphate, magnesium stearate, macrogol, titanium dioxide, iron oxide red.

6.2 Incompatibilities

Not applicable

6.3 Shelf life

3 years

6.4 Special precautions for storage

Store below 25°C.

6.5 Nature and contents of container

Supplied in packs of 60 and 112 tablets.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Any unused medicine or waste material should be disposed of in accordance with local requirements.

7 MEDICINE SCHEDULE

Prescription Medicine

8 SPONSOR

Bayer New Zealand Limited

PO Box 2825
Shortland Street
Auckland 1140
New Zealand

Free Phone 0800 233 988

www.bayer.co.nz

9 DATE OF FIRST APPROVAL

31 May 2007

10 DATE OF REVISION OF THE TEXT

24 August 2023

SUMMARY TABLE OF CHANGES

Section Changed	Summary of New Information
Section 3 Pharmaceutical form	Update to tablet description