SCHEDULING STATUS: S4

PROPRIETARY NAME AND DOSAGE FORM:

NEXAVAR® 200
Film-coated Tablets

COMPOSITION:

Each NEXAVAR® 200 film-coated tablet contains 200 mg of sorafenib (274 mg sorafenib tosylate). Other excipients include; croscarmellose sodium, microcrystalline cellulose, hydroxypropylmethyl cellulose, sodium lauryl sulphate, magnesium stearate, macrogol, titanium dioxide, iron oxide red.

PHARMACOLOGICAL CLASSIFICATION:

A 26. Cytostatic Agents

PHARMACOLOGICAL ACTION:

Pharmacodynamic properties:

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

Pharmacokinetic properties:

Absorption and distribution:
After administration of sorafenib tablets, the mean relative bioavailability is 38 to 49 % when compared to an oral solution. 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.

In vitro binding of sorafenib to human plasma proteins is 99,5 %.

Metabolism/Biotransformation:
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 gastrointestinal tract by bacterial glucuronidase activity, allowing reabsorption of unconjugated medicine. Co-administration of neomycin interferes with this process, decreasing the mean bioavailability of sorafenib by 54 %.

Sorafenib accounts for approximately 70 to 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 to 16 % of circulating analytes at steady state.

Elimination/Excretion:
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. The elimination half-life of sorafenib is approximately 25 to 48 hours.

Steady state pharmacokinetics:

Multiple dosing of sorafenib for 7 days results in a 2, 5 to 7 fold accumulation compared to single dose administration. Steady state-plasma sorafenib concentrations are achieved within 7 days, with a peak to trough-ratio of mean concentrations of less than 2.

The steady-state pharmacokinetics of sorafenib administered at 400 mg twice daily was evaluated in thyroid carcinoma, RCC and HCC patients. The highest mean exposure was observed in thyroid carcinoma patients, though variability in exposure was high for all tumor types. The clinical relevance of the increased AUC in thyroid carcinoma patients is unknown.

Steady state plasma sorafenib AUC (0-12)ss from differentiated thyroid carcinoma, RCC and HCC patients (geometric mean (% CV) [range].

	Thyroid Cancer pool	**RCC pool**	**HCC pool**
AUC (0-12)ss (mg*h/L)	74,99 (45 %) [29,03 to 186,2] N = 114	39,36 (45 %) [10,69 to 103, 9] N = 136	44,98 (52 %) [9,94 to 242,0] N = 194

Studies on enzyme inhibition:
Studies with human liver microsomes demonstrated that sorafenib is a competitive inhibitor of CYP2C19, CYP2D6 and CYP3A4.
In vitro data show that sorafenib inhibits glucuronidation by the UGT1A1 and UGT1A9 pathways.
Sorafenib inhibits CYP2B6 and CYP2C8 *in vitro* with Ki values of 6 and 1 to 2 µM, respectively.

Concomitant administration of sorafenib with cyclophosphamide resulted in a 25 % decrease in cyclophosphamide exposure, and a 30 % increase 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.

Studies with human liver microsomes demonstrated that sorafenib is a competitive inhibitor of CYP2C9 with a Ki value of 7 to 8 µM. The possible effect of sorafenib on a CYP2C9 substrate was assessed in patients receiving sorafenib or placebo in combination with warfarin. The mean changes from baseline in PT-INR were not higher in sorafenib patients compared to placebo patients, suggesting that sorafenib may not be an *in vivo* inhibitor of CYP2C9.

Effect of 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.

INDICATIONS:

NEXAVAR® 200 film-coated tablets are indicated for the;

- Treatment of patients with advanced renal cell carcinoma (RCC).
- Treatment of patients with advanced inoperable hepatocellular carcinoma (HCC)
- Treatment of patients with locally advanced or metastatic differentiated (papillary and follicular-Hürthle cell) thyroid carcinoma refractory to radioactive iodine.

CONTRA-INDICATIONS:

NEXAVAR® 200 is contra-indicated in patients with known severe hypersensitivity to sorafenib or any of the excipients.
Pregnancy and lactation (see “Pregnancy and Lactation”).

WARNINGS AND SPECIAL PRECAUTIONS:

Dermatological Toxicities:

Hand-foot skin reaction (palmar-plantar erythrodysaesthesia) and rash represent the most common adverse drug reactions with NEXAVAR® 200. 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® 200. Management of dermatologic toxicities may include topical therapies for symptomatic relief; temporary treatment interruption and/or dose modification of NEXAVAR® 200, or in severe or persistent cases, permanent discontinuation of NEXAVAR® 200 (see "Side effects").

Hypertension:

An increased incidence of hypertension was observed in NEXAVAR® 200-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® 200 should be considered (see "Side effects").

Haemorrhage:

An increase in the risk of bleeding may occur following NEXAVAR® 200 administration. The incidence of severe bleeding events is uncommon. If any bleeding event necessitates medical intervention, it is recommended that permanent discontinuation of NEXAVAR® 200 should be considered (see "Side effects"). Due to the potential risk of bleeding, tracheal, bronchial and oesophageal infiltration should be treated with localised therapy prior to administering NEXAVAR® 200 in patients with differentiated thyroid carcinoma.

Warfarin:

Bleeding events or elevations in the International Normalised Ratio (INR) have been reported in some patients taking warfarin while on NEXAVAR® 200 therapy. Patients taking warfarin concomitantly should be monitored regularly for changes in prothrombin time/INR and for clinical bleeding episodes (see "Side effects" and "Interactions").

Wound healing complications:

No formal studies of the effect of NEXAVAR® 200 on wound healing have been conducted. In patients undergoing major surgical procedures, temporary interruption of NEXAVAR® 200 therapy is recommended for precautionary reasons. There is limited clinical experience regarding the timing of reinitiation of therapy following major surgical intervention. Therefore, the decision to resume NEXAVAR® 200 therapy following a major surgical intervention should be based on clinical judgment of adequate wound healing.

Cardiac Ischaemia and/or Infarction:

In Study 11213 (renal cell carcinoma), the incidence of treatment-emergent cardiac ischaemia/infarction events was higher in the NEXAVAR® 200 group (4.9 %) compared with the placebo group (0,4 %). In Study 100554 (hepatocellular carcinoma), the incidence of treatment-emergent cardiac ischaemia/infarction events was 2,7 % in NEXAVAR® 200 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® 200 should be considered in patients who develop cardiac ischaemia and/or infarction.

QT interval prolongation:

NEXAVAR® 200 has been shown to prolong the QT/QTc interval on the ECG, which may lead to an increased risk for ventricular dysrhythmias. Use NEXAVAR® 200 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-dysrhythmic medicines or other medicinal products that lead to QT prolongation, and those with electrolyte disturbances such as hypokalaemia, hypocalcaemia, or hypomagnesaemia. When using NEXAVAR® 200 in these patients, periodic monitoring with on-treatment electrocardiograms and electrolytes (magnesium, potassium, calcium) should be considered.

Gastrointestinal perforation:

Gastrointestinal perforation has been reported in less than 1 % of patients taking NEXAVAR® 200. In some cases this was not associated with apparent intra-abdominal tumour. NEXAVAR® 200 therapy should be discontinued (see "Side effects").

Hepatic impairment:

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.

Hypocalcaemia:

When using NEXAVAR® 200 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 "Side effects").

TSH Suppression in Differentiated Thyroid Carcinoma (DTC):

In the DTC clinical trials, increases in TSH levels above 0,5 mU/L were observed in NEXAVAR® 200 treated patients. When using NEXAVAR® 200 in differentiated thyroid carcinoma patients, close monitoring of TSH levels is recommended.

Interactions:

UGT1A pathway

Caution is recommended when administering NEXAVAR® 200 together with compounds that are metabolised/eliminated predominantly by the UGT1A1 pathway (e.g. irinotecan).

Docetaxel

NEXAVAR® 200 has not been evaluated for use in HCC in combination with docetaxel, paclitaxel and carboplatin.

Neomycin

Co-administration of neomycin, a non-systemic antimicrobial agent used to eradicate gastrointestinal flora, interferes with the enterohepatic recycling of sorafenib, 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.

Effects on ability to drive and use machines:

The development of peripheral sensory neuropathy may affect the ability to drive or to operate machinery.

INTERACTIONS:

CYP3A4 inducers:

Continuous concomitant 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 increase metabolism of sorafenib and thus decrease sorafenib concentrations.

CYP3A4 inhibitors:

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

CYP2C9 substrates:

The possible effect of sorafenib on warfarin, a CYP2C9 substrate, was assessed in NEXAVAR® 200-treated patients compared to placebo treated patients. The concomitant treatment with NEXAVAR® 200 and warfarin did not result in changes in mean PT-INR compared to placebo. However, patients taking warfarin should have their INR checked regularly.

CYP isoform-selective substrates:

Concomitant administration of midazolam, dextromethorphan and omeprazole, which are substrates of cytochromes CYP3A4, CYP2D6 and CYP2C19, respectively, following 4 weeks of NEXAVAR® 200 administration did not alter the exposure of these agents. This indicates that NEXAVAR® 200 is neither an inhibitor nor an inducer of these cytochrome P450 isoenzymes. In a separate clinical study, concomitant administration of sorafenib with paclitaxel resulted in an increase, instead of a decrease, in the exposure of 6-OH paclitaxel, the active metabolite of paclitaxel that is formed by CYP2C8. These data suggest that sorafenib may not be an *in vivo* inhibitor of CYP2C8.
In another clinical study, concomitant administration of sorafenib with cyclophosphamide resulted in a 25 % decrease in cyclophosphamide exposure, and a 30 % increase 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® 200 has been administered together with a variety of other anti-neoplastic agents at their commonly used dosing regimens, including gemcitabine, oxaliplatin, paclitaxel, carboplatin, capecitabine, doxorubicin, irinotecan, docetaxel and cyclophosphamide. NEXAVAR® 200 had no clinically relevant effect on the pharmacokinetics of gemcitabine, carboplatin, oxaliplatin or cyclophosphamide.

Paclitaxel/Carboplatin:

Administration of paclitaxel (225 mg/m^2) and carboplatin (AUC = 6) with NEXAVAR® 200 (≤ 400 mg twice daily), administered with a 3-day break in NEXAVAR® 200 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 NEXAVAR® 200 (400 mg twice daily, without a break in sorafenib dosing) resulted in a 47 % increase in NEXAVAR® 200 exposure, a 29 % increase in paclitaxel exposure and a 50 % increase in 6-OH paclitaxel exposure. The pharmacokinetics of carboplatin was unaffected.
These data indicate no need for dose adjustments when paclitaxel and carboplatin are co-administered with NEXAVAR® 200 with a 3-day break in NEXAVAR® 200 dosing. The clinical significance of the increases in NEXAVAR® 200 and paclitaxel exposure, upon co-administration of NEXAVAR® 200 without a break in dosing, is unknown.

Capecitabine:

Co-administration of capecitabine (750 to 1050 mg/m^2 twice daily, Days 1 to 14 every 21 days) and NEXAVAR® 200 (200 or 400 mg twice daily, continuous uninterrupted administration) resulted in no significant change in NEXAVAR® 200 exposure, but a 15 to 50 % increase in capecitabine exposure and a 0 to 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 NEXAVAR® 200 is unknown.

Doxorubicin/Irinotecan:

Concomitant treatment with NEXAVAR® 200 resulted in a 21 % increase in the AUC of doxorubicin. When administered with irinotecan, whose active metabolite SN-38 is further metabolised by the UGT1A1 pathway, there was a 67 to 120 % increase in the AUC of SN-38 and a 26 to 42 % increase in the AUC of irinotecan. The clinical significance of these findings is unknown.

Omeprazole:

Co-administration of omeprazole has no impact on the pharmacokinetics of NEXAVAR® 200. No dose adjustment for NEXAVAR® 200 is necessary.

Warfarin:

Bleeding events or elevations in the International Normalised Ratio (INR) have been reported in some patients taking warfarin while on NEXAVAR® 200 therapy. Patients taking warfarin concomitantly should be monitored regularly for changes in prothrombin time/INR and for clinical bleeding episodes (see "Side-effects").

PREGNANCY AND LACTATION:

Pregnancy:

Women should avoid becoming pregnant while on therapy with NEXAVAR® 200. Women of childbearing potential must be apprised of the potential hazard to the foetus, which includes severe malformation (teratogenicity), failure to thrive and foetal death (embryotoxicity). NEXAVAR® 200 should not be used during pregnancy.
Adequate contraception should be used during therapy and for at least 2 weeks after completion of therapy.

Breastfeeding:

Breastfeeding should be discontinued during NEXAVAR® 200 therapy. Infants should not be breastfed during treatment with NEXAVAR® 200.

DOSAGE AND DIRECTIONS FOR USE:

Recommended dose:

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

Method of administration:

For oral use. To be swallowed with a glass of water.

Duration of treatment:

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

Dose titration, dose adjustment, special monitoring advice:

Dose reduction for hepatocellular carcinoma and advanced renal cell carcinoma:

Management of suspected adverse reactions may require temporary interruption and/or dose reduction of NEXAVAR® 200 therapy. When dose reduction is necessary during treatment of hepatocellular carcinoma (HCC) and advanced renal carcinoma (RCC), the NEXAVAR® 200 dose should be reduced to 400 mg daily.
Suggested dose modifications for skin toxicity with HCC and RCC:

Grade	Occurrence	NEXAVAR® 200 dose modification
Grade 1 (mild)	Any	Institute *supportive measures* immediately and continue NEXAVAR® 200 treatment
Grade 2 (moderate)	First	Institute *supportive measures* immediately and consider a decrease NEXAVAR® 200 dose to 400 mg daily for 28 days

		• If toxicity returns to grade 0 to 1 after dose reduction, increase NEXAVAR® 200 to full dose after 28 days If toxicity does not return to grade 0 to 1 despite dose reduction, interrupt NEXAVAR® 200 treatment for a minimum of 7 days, until toxicity has resolved to grade 0 to 1 • When resuming treatment after dose interruption, resume NEXAVAR® 200 at reduced dose of 400 mg daily for 28 days • If toxicity is maintained at grade 0 to 1 at reduced dose, increase NEXAVAR® 200 to full dose after 28 days
	Second or Third	As for first occurrence, but upon resuming NEXAVAR® 200 treatment, decrease dose to 400 mg daily indefinitely
	Fourth	Discontinue NEXAVAR® 200 treatment
Grade 3 (severe)	First	Institute *supportive measures* immediately and interrupt NEXAVAR® 200 treatment for a minimum of 7 days and until toxicity has resolved to grade 0 to 1 • When resuming treatment after dose interruption, resume NEXAVAR® 200 at reduced dose of 400 mg daily for 28 days • If toxicity is maintained at grade 0 to 1 at reduced dose, increase NEXAVAR® 200 to full dose after 28 days
	Second	As for first occurrence, but upon resuming NEXAVAR® 200 treatment, decrease dose to 400 mg daily indefinitely
	Third	Discontinue NEXAVAR® 200 treatment.

Dose Reduction for Differentiated Thyroid Carcinoma:

Management of suspected side-effects may require temporary interruption and/or dose reduction of NEXAVAR® 200 therapy. When dose reduction is necessary during the treatment of differentiated thyroid carcinoma, the NEXAVAR® 200 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® 200 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 sorafenib may be increased.

Special Populations:

Paediatric patients:

The safety and effectiveness of NEXAVAR® 200 in paediatric patients has not been established.

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.

Hepatic impairment:

No dose adjustment is required in patients with Child-Pugh A or B hepatic impairment. NEXAVAR® 200 has not been studied in patients with Child-Pugh C hepatic impairment.

Renal impairment:

No dose adjustment is required in patients with mild, moderate or severe renal impairment not requiring dialysis. NEXAVAR® 200 has not been studied in patients undergoing dialysis.
Monitoring of fluid balance and electrolytes in patients at risk of renal dysfunction is advised.

SIDE-EFFECTS:

Postmarketing Adverse Experience:

The following adverse medicine reactions have been identified during post-approval use of NEXAVAR® 200.

System Organ Class	Unknown frequency
Dermatologic:	Radiation recall dermatitis
Hypersensitivity:	Angioedema
Skin and Subcutaneous Tissue Disorders:	Stevens-Johnson syndrome, Leukocytoclastic vasculitis, Toxic epidermal necrolysis.
Musculoskeletal, Connective Tissue and Bone Disorders:	Rhabdomyolysis

Laboratory test abnormalities in renal cell carcinoma patients (study 11213):

Laboratory test abnormalities in hepatocellular carcinoma patients (study 100554):

Laboratory abnormalities	Very Common ≥ 1/10		Common ≥ 1/100 to < 1/10		Uncommon ≥ 1/1000 to < 1/100	
	Sorafenib group (%)	Placebo group (%)	Sorafenib group (%)	Placebo group (%)	Sorafenib group (%)	Placebo group (%)
Lipase elevated grades 3 or 4	12 %	7 %				
Hypophosphataemia (general):	45 %	11 %				
CTCAE grade 3 Hypophosphataemia	13 %	3 %				
CTCAE grade 3 or 4 Lymphopenia	13 %	7 %				
CTCAE grade 3 or 4 Amylase elevation			1 %	3 %		
CTCAE grade 3 or 4 Neutropenia			5 %	2 %		
CTCAE grade 3 or 4 Anaemia			2 %	4 %		
CTCAE grade 3 or 4 Thrombocytopenia			1 %	0 %		
Hypocalcaemia (general):			12 %	7,5 %		
CTCAE grade 3 Hypocalcaemia			1,1 %	0,2 %		
CTCAE grade 4 Hypocalcaemia			1,3 %	0,5 %		
Hypokalemia (general):			5,4 %	0,7 %		
CTCAE grade 3 Hypokalemia			1,3 %	0,2 %		
Clinical pancreatitis					0,4 %	0,2 %

Laboratory abnormalities	Very Common ≥ 1/10		Common ≥ 1/100 to < 1/10		Uncommon ≥ 1/1000 to < 1/100	
	Sorafenib group (%)	Placebo group (%)	Sorafenib group (%)	Placebo group (%)	Sorafenib group (%)	Placebo group (%)
Lipase elevation (general)	40 %	37 %				
CTCAE grade 3 or 4 Lipase elevation	9 %	9 %				
Amylase elevation (general):	34 %	29 %				
Amylase elevation			2 %	2 %		
Hypophosphataemia (general):	35 %	11 %				

Laboratory abnormalities	**Very Common ≥ 1/10**		**Common ≥ 1/100 to < 1/10**		**Uncommon ≥ 1/1000 to < 1/100**	
	Sorafenib group (%)	Placebo group (%)	Sorafenib group (%)	Placebo group (%)	Sorafenib group (%)	Placebo group (%)
CTCAE grade 3 Hypophosphataemia	11 %	2 %				
AST elevation (general):	94 %	91 %				
CTCAE grade 3 or 4 AST elevation	16 %	17 %				
ALT elevation (general):	69 %	68 %				
CTCAE grade 3 or 4 ALT elevation	3 %	8 %				
Bilirubin elevation (general):	47 %	45 %				
CTCAE grade 3 or 4 Bilirubin elevation	10 %	11%				
Hypoalbuminaemia (general):	59 %	47%				
CTCAE grade 3 or 4 Hypoalbuminaemia:	0	0				
INR elevation (general):	42 %	34 %				
CTCAE grade 3 INR elevation			4 %	2 %		
CTCAE grade 4 INR elevation			0	0		
Lymphopenia (general):	47 %	42 %				
CTCAE grade 3 or 4 Lymphopenia	6 %	6 %				
General Neutropenia	11 %	14 %				
CTCAE grade 3 or 4 Neutropenia	1 %	1 %				
Anaemia (general):	59 %	64 %				
CTCAE grade 3 or 4 Anaemia			3 %	3 %		
Thrombocytopenia (general):	46 %	41 %				
CTCAE grade 3 or 4 Thrombocytopenia			4 %	1 %		
Hypocalcaemia (general):	26,5 %	14,8 %				
CTCAE grade 3 Hypocalcaemia			1,8 %	1,1 %		
CTCAE grade 4 Hypocalcaemia					0,4 %	0 %
Hypokalemia (general):			9,4 %	5,9 %		
CTCAE grade 3 Hypokalemia					0,3 %	0,7 %
Clinical pancreatitis					0,3 %	0 %

Laboratory test abnormalities in thyroid carcinoma patients:

	Very Common	**Common**	**Uncommon**

Laboratory abnormalities	≥ 1/10		≥ 1/100 to < 1/10		≥ 1/1000 to < 1/100	
	Sorafenib group (%)	Placebo group (%)	Sorafenib group (%)	Placebo group (%)	Sorafenib group (%)	Placebo group (%)
Hypocalcaemia (general):	35,7 %	11				
CTCAE grade 3 Hypocalcaemia			6,8 %	1,9 %		
CTCAE grade 4 Hypocalcaemia			3,4 %	1,0 %		

Other clinically relevant laboratory abnormalities observed in the study are shown here:

Laboratory parameter, (in % of samples investigated)	NEXAVAR® 200 N=207			Placebo N = 209		
	All grades	Grade 3	Grade 4	All grades	Grade 3	Grade 4
Blood and lymphatic system disorders:						
Anaemia	30,9	0, 5	0	23,4	0,5	0
Thrombocytopaenia	18,4	0	0	9,6	0	0
Neutropenia	19,8	0,5	0,5	12	0	0
Lymphopenia	42	9,7	0,5	25,8	5,3	0
Metabolism and nutrition disorders:						
Hypokalaemia	17,9	1,9	0	2,4	0	0
Hypophosphatemia	19,3	12,6	0	2,4	1,4	0
Hepatobilliary disorders:						
Increased bilirubin	8,7	0	0	4,8	0	0
Increased ALT	58,9	3,4	1,0	24,4	0	0
Increased AST	53,6	1,0	1,0	14,8	0	0
Investigations:						
Increased amylase	12,6	2,4	1,4	6,2	0	1,0
Increased lipase	11,1	2,4	0	2,9	0,5	0
*Common Terminology Criteria for Adverse Events (CTCAE), Version 3						
** The aetiology of hypophosphatemia associated with NEXAVAR® 200 is not known						

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:

There is no specific treatment for NEXAVAR® 200 overdose. The highest dose of NEXAVAR® 200 studied clinically is 800 mg twice daily. The adverse reactions observed at this dose were primarily diarrhoea and dermatologic events.
In the event of suspected overdose, NEXAVAR® 200 should be withheld and supportive care instituted.

IDENTIFICATION:

Red round, faceted biconvex film coated tablet, with Bayer cross on one side and “200” on the other side.

PRESENTATION:

Aluminium (Al) blister packs of 60 tablets, with each carton containing 6 blister strips of 10 tablets; or aluminium (Al) blister packs of 112 tablets, with each carton containing 8 blister strips of 14 tablets.

STORAGE INSTRUCTIONS:

Store at or below 30 °C in a dry place. Store in the manufacturer's original container.
KEEP OUT OF REACH OF CHILDREN.

REGISTRATION NUMBER:

A40/26/0776

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION:

Bayer (Pty) Ltd
Registration No.: 1968/011192/07
27 Wrench Road
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1609

DATE OF PUBLICATION OF THIS PACKAGE INSERT:
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