APPROVED PROFESSIONAL INFORMATION

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

SORAFENIB 200 DRL film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each SORAFENIB 200 DRL film-coated tablet contains 200 mg of sorafenib (274 mg sorafenib tosylate).

Sugar free.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.

Red, round, biconvex, film-coated tablets, debossed with "S" on one side and plain on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

SORAFENIB 200 DRL 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.

4.2 Posology and method of administration

Posology

Recommended dose:

The recommended daily dose of SORAFENIB 200 DRL 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.

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 interruptions and/or dose reduction of SORAFENIB 200 DRL therapy. When dose reduction is necessary during treatment of hepatocellular carcinoma (HCC) and advanced renal carcinoma (RCC), the SORAFENIB 200 DRL dose should be reduced to 400 mg daily.

Suggested dose modifications for skin toxicity with HCC and RCC:

	Occurrence	**SORAFENIB 200 DRL dose modification**
Grade 1 (mild)	Any	Institute supportive measures immediately and continue SORAFENIB 200 DRL treatment
Grade 2 (moderate)	First	Institute supportive measures immediately and consider a decrease SORAFENIB 200 DRL dose to 400 mg daily for 28 days. • If toxicity returns to grade 0 to 1 after dose reduction, increase SORAFENIB 200 DRL to full dose after 28 days. If toxicity does not return to grade 0 to 1 despite' dose reduction, interrupt SORAFENIB 200 DRL treatment for a minimum of 7 days, until toxicity has resolved to grade 0 to 1 • When resuming treatment after dose interruption, resume SORAFENIB 200 DRL at reduced dose of 400 mg daily for 28 days • If toxicity is maintained at grade 0 to 1 at reduced dose, increase SORAFENIB 200 DRL to full dose after 28 days
	Second or third	As for first occurrence, but upon resuming SORAFENIB 200 DRL treatment, decrease dose to 400 mg daily indefinitely
	Fourth	Discontinue SORAFENIB 200 DRL treatment

Grade 3 (severe)	First	Institute supportive measures immediately and interrupt SORAFENIB 200 DRL treatment for a minimum of 7 days and until toxicity has resolved to grade 0 to 1 • When resuming treatment after dose interruption, resume SORAFENIB 200 DRL at reduced dose of 400 mg daily for 28 days • If toxicity is maintained at grade 0 to 1 at reduced dose, increase SORAFENIB 200 DRL to full dose after 28 days
	Second	As for first occurrence, but upon resuming SORAFENIB 200 DRL treatment, decrease dose to 400 mg daily indefinitely
	Third	Discontinue SORAFENIB 200 DRL treatment

Dose Reduction for Differentiated Thyroid Carcinoma:

Management of suspected side-effects may require temporary interruption and/or dose reduction of SORAFENIB 200 DRL therapy.

When dose reduction is necessary during the treatment of differentiated thyroid carcinoma, the SORAFENIB 200 DRL 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, SORAFENIB 200 DRL 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 SORAFENIB 200 DRL 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. SORAFENIB 200 DRL 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. SORAFENIB 200 DRL has not been studied in patients undergoing dialysis.

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

Method of administration:

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

4.3 Contraindications

- SORAFENIB 200 DRL is contraindicated in patients with known severe hypersensitivity to sorafenib or any of the excipients in section 6.1.
- Pregnancy and lactation (see section 4.6).

4.4 Special warnings and precautions for use

Dermatological toxicities:

Hand foot skin reaction (palmar-plantar erythrodysaesthesia) and rash represent the most common adverse drug reactions with SORAFENIB 200 DRL. 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 SORAFENIB 200 DRL. Management of dermatological toxicities may include topical therapies for symptomatic relief, temporary treatment interruption and/or dose modification of SORAFENIB 200 DRL, or in severe or persistent cases, permanent discontinuation of SORAFENIB 200 DRL (see section 4.8).

Hypertension:

An increased incidence of arterial hypertension was observed in SORAFENIB 200 DRL-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 institution of antihypertensive therapy, permanent discontinuation of SORAFENIB 200 DRL should be considered (see section 4.8).

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 SORAFENIB 200 DRL, this risk should be carefully considered in patients with risk factors such as hypertension or history of aneurysm.

Hypoglycaemia:

Decreases in blood glucose, in some cases clinically symptomatic and requiring hospitalization due to loss of consciousness, have been reported during sorafenib

as in SORAFENIB 200 DRL treatment. In case of symptomatic hypoglycaemia, SORAFENIB 200 DRL should be temporarily interrupted. Blood glucose levels in diabetic patients should be checked regularly in order to assess if anti-diabetic medicines dosage needs to be adjusted.

Haemorrhage:

An increased risk of bleeding may occur following SORAFENIB 200 DRL administration.

The incidence of severe bleeding events is uncommon.

If any bleeding event necessitates medical intervention, it is recommended that permanent discontinuation of SORAFENIB 200 DRL should be considered (see section 4.8).

Cardiac ischaemia and/or infarction:

In a renal cell carcinoma study, the incidence of treatment-emergent cardiac ischaemia/infarction events was higher in the sorafenib group (4,9 %) compared with the placebo group (0,4 %).

In a hepatocellular carcinoma study, 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 SORAFENIB 200 DRL should be considered in patients who develop cardiac ischaemia and/or infarction (see section 4.8).

QT interval prolongation:

SORAFENIB 200 DRL has been shown to prolong the QT/QTc interval on the ECG, which may lead to an increased risk for ventricular dysrhythmias. Use

SORAFENIB 200 DRL 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 medicines that lead to QT prolongation, and those with electrolyte disturbances such as hypokalaemia, hypocalcaemia, or hypomagnesaemia. When using SORAFENIB 200 DRL 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 sorafenib as in SORAFENIB 200 DRL. In some cases, this was not associated with apparent intra-abdominal tumour. SORAFENIB 200 DRL therapy should be discontinued (see section 4.8).

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 (see section 4.2).

Warfarin co-administration:

Infrequent bleeding events or elevations in the International Normalised Ratio (INR) have been reported in some patients taking warfarin while on sorafenib therapy. Patients taking concomitant warfarin or phenprocoumon should be monitored regularly for changes in prothrombin time, INR or clinical bleeding episodes (see sections 4.5 and 4.8).

Wound healing complications:

No formal studies of the effect of SORAFENIB 200 DRL on wound healing have been conducted. Temporary interruption of SORAFENIB 200 DRL therapy is

recommended for precautionary reasons in patients undergoing major surgical procedures. There is limited clinical experience regarding the timing of reinitiation of therapy following major surgical intervention. Therefore, the decision to resume SORAFENIB 200 DRL therapy following a major surgical intervention should be based on clinical judgement of adequate wound healing.

Elderly population:

Cases of renal failure have been reported. Monitoring of renal function should be considered.

Medicine-medicine interactions:

Caution is recommended when administering SORAFENIB 200 DRL with compounds that are metabolised/eliminated predominantly by the UGT1A1 (e.g. irinotecan) or UGT1A9 pathways (see section 4.5).

Caution is recommended when SORAFENIB 200 DRL is co-administered with docetaxel (see section 4.5).

Co-administration of neomycin or other antibiotics that cause major ecological disturbances of the gastrointestinal microflora may lead to a decrease in sorafenib bioavailability (see section 4.5). The risk of reduced plasma concentrations of sorafenib should be considered before starting a treatment course with antibiotics.

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

Disease specific warnings:

Differentiated thyroid cancer (DTC)

Before initiating treatment, physicians are recommended to carefully evaluate the prognosis in the individual patient considering maximum lesion size, symptoms related to the disease and progression rate.

Management of suspected adverse drug reactions may require temporary

interruption or dose reduction of sorafenib therapy. Dose reductions have been shown to be only partially successful in alleviating adverse reactions. Therefore repeat evaluations of benefit and risk is recommended taking anti-tumour activity and tolerability into account.

Haemorrhage in DTC

Due to the potential risk of bleeding, tracheal, bronchial, and oesophageal infiltration should be treated with localized therapy prior to administering sorafenib in patients with DTC.

Hypocalcaemia in DTC

When using SORAFENIB 200 DRL 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 section 4.8). Severe hypocalcaemia should be corrected to prevent complications such as QT-prolongation or torsade de pointes (see section QT prolongation).

TSH suppression in DTC

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

Renal cell carcinoma

High Risk Patients, according to MSKCC (Memorial Sloan Kettering Cancer Center) prognostic group, were not included in the phase III clinical study in renal cell carcinoma, and benefit-risk in these patients has not been evaluated.

Information about excipients:

This medicine contains less than 1 mmol sodium (23 mg) per dose, that is to say

essentially "sodium free".

4.5 Interaction with other medicines and other forms of interaction

Inducers of metabolic enzymes:

Administration of rifampicin for 5 days before administration of a single dose of sorafenib resulted in an average 37 % reduction of sorafenib AUC.

Other inducers of CYP3A4 activity and/or glucuronidation (e.g. *Hypericum perforatum* also known as St. John's wort, phenytoin, carbamazepine, phenobarbital, and dexamethasone) may also increase metabolism of sorafenib and thus decrease sorafenib concentrations.

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. These data suggest that clinical pharmacokinetic interactions of sorafenib with CYP3A4 inhibitors are unlikely.

CYP2B6, CYP2C8 and CYP2C9 substrates:

Sorafenib inhibited CYP2B6, CYP2C8 and CYP2C9 *in vitro* with similar potency. However, in clinical pharmacokinetic studies, concomitant administration of sorafenib 400 mg twice daily with cyclophosphamide, a CYP2B6 substrate, or paclitaxel, a CYP2C8 substrate, did not result in a clinically meaningful inhibition. These data suggest that sorafenib at the recommended dose of 400 mg twice daily may not be an *in vivo* inhibitor of CYP2B6 or CYP2C8.

Additionally, concomitant treatment with sorafenib and warfarin, a CYP2C9 substrate, did not result in changes in mean PT-INR compared to placebo. Thus, also the risk for a clinically relevant *in vivo* inhibition of CYP2C9 by SORAFENIB 200 DRL maybe expected to be low. However, patients taking warfarin or phenprocoumon should have their INR checked regularly (see section 4.4).

CYP3A4, CYP2D6 and CYP2C19 substrates:

Concomitant administration of midazolam, dextromethorphan and omeprazole, which are substrates of cytochromes CYP3A4, CYP2D6 and CYP2C19, respectively, following 4 weeks of sorafenib administration did not alter the exposure of these medicines. This indicates that SORAFENIB 200 DRL is neither an inhibitor nor an inducer of these cytochrome P450 isoenzymes. Therefore, clinical pharmacokinetic interactions of sorafenib with substrates of these enzymes are unlikely.

UGT1A1 and UGT1A9 substrates:

In vitro, sorafenib inhibited glucuronidation via UGT1A1 and UGT1A9. The clinical relevance of this finding is unknown (see below and section 4.4).

***In vitro* studies of CYP enzyme induction:**

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

P-gp-substrates

In vitro, sorafenib has been shown to inhibit the transport protein p-glycoprotein (P-gp). Increased plasma concentrations of P-gp substrates such as digoxin cannot be excluded with concomitant treatment with SORAFENIB 200 DRL.

Combination with other anti-neoplastic medicines:

In clinical studies sorafenib has been administered with a variety of other anti-neoplastic medicines at their commonly used dosing regimens including gemcitabine, cisplatin, oxaliplatin, paclitaxel, carboplatin, capecitabine, doxorubicin, irinotecan, docetaxel and cyclophosphamide. Sorafenib 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 (two days prior to and on the day of paclitaxel/carboplatin administration), 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 200 DRL with a 3-day break in SORAFENIB 200 DRL dosing (two days prior to and on the day of paclitaxel/carboplatin administration). 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 sorafenib 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 - 120 % increase in the AUC of SN-38 and a 26 - 42 % increase in the AUC of irinotecan. The clinical significance of these findings is unknown (see section 4.4).

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 SORAFENIB 200 DRL is co-administered with docetaxel (see section 4.4).

Omeprazole:

Co-administration of omeprazole has no impact on the pharmacokinetics of sorafenib as in SORAFENIB 200 DRL. No dose adjustment for SORAFENIB 200 DRL is necessary.

Combination with other medicines:

Neomycin

Co-administration of neomycin, a non-systemic antimicrobial agent used to eradicate gastrointestinal flora, interferes with the enterohepatic recycling of sorafenib (see section 5.2, Metabolism and Elimination), resulting in decreased sorafenib exposure. In healthy volunteers treated with a 5-day regimen of neomycin the average exposure to 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 interfere with microorganisms with glucuronidase activity.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential

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).

Pregnancy

Women should avoid becoming pregnant while on therapy with SORAFENIB 200 DRL.

SORAFENIB 200 DRL should not be used during pregnancy.

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

Lactation

Breastfeeding should be discontinued during SORAFENIB 200 DRL therapy.

Infants should not be breastfed during treatment with SORAFENIB 200 DRL.

Fertility

Results from animal studies further indicate that sorafenib can impair male and female fertility.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

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

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

Tabulated list of adverse reactions

System Organ Class	**Frequent**	**Less frequent**	**Frequency not known**
Infections and infestations:	Infection, folliculitis		
Blood and the lymphatic system disorders:	lymphopenia, leucopenia, neutropenia, anaemia, thrombocytopenia		
Immune system disorders:		hypersensitivity reactions (including skin reactions and urticaria), anaphylactic reaction, angioedema	
Endocrine Disorders:	hypothyroidism	hyperthyroidism	
Metabolism and nutrition disorders:	Anorexia, hypo-phosphataemia, hypocalcaemia,	dehydration	

	hypokalaemia, hyponatraemia, hypoglycaemia		
Psychiatric disorders:		depression	
Nervous system disorders:	peripheral sensory neuropathy, dysgeusia	reversible posterior leukoencephalopathy*	encepha-lopathy
Ear and labyrinth disorders:	tinnitus		
Cardiac disorders:	congestive heart failure*, myocardial ischaemia and infarction*	QT prolongation	
Vascular disorders:	haemorrhage (inc. gastrointestinal*, respiratory tract* and cerebral haemorrhage*), hypertension, flushing	hypertensive crisis*	aneurysms and artery dissections

Respiratory, thoracic and mediastinal disorders:	Rhinorrhoea, dysphonia	interstitial lung disease-like events* (pneumonitis, radiation pneumonitis, acute respiratory distress, etc.)	
Gastrointestinal disorders:	diarrhoea, nausea, vomiting, constipation, stomatitis (including dry mouth and glossodynia), dyspepsia, dysphagia, gastro oesophageal reflux disease	pancreatitis, gastritis, gastrointestinal perforations*	
Hepatobiliary disorders:		increase in bilirubin and jaundice,	

		cholecystitis, cholangitis, drug induced hepatitis*	
Skin and subcutaneous tissue disorders:	dry skin, rash, alopecia, hand foot skin reaction**, erythema, pruritus, keratoacanthoma/ squamous cell cancer of the skin, dermatitis exfoliative, acne, skin desquamation, hyperkeratosis	eczema, erythema multiforme, radiation recall dermatitis, Stevens Johnson syndrome, leucocytoclastic vasculitis, toxic epidermal necrolysis*	
Musculoskeletal and connective tissue disorders:	arthralgia, myalgia, muscle spasms	rhabdomyolysis	
Renal and	renal failure,	nephrotic	

urinary disorders:	proteinuria	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.

** Hand foot skin reaction corresponds to palmar plantar erythrodysaesthesia syndrome in MedDRA.

In clinical trials, certain adverse drug reactions such as hand – foot skin reaction, diarrhoea, alopecia, weight decrease, hypertension, hypocalcaemia and keratocanthoma/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. Health care providers are requested to report any suspected adverse drug reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

4.9 Overdose

There is no specific treatment for SORAFENIB 200 DRL overdose. The highest dose of sorafenib 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, SORAFENIB 200 DRL should be withheld and supportive care instituted.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacological classification: A 26 Cytostatic agents

Pharmacotherapeutic group: Antineoplastic agents, protein kinase inhibitors, ATC code: L01XE05

Mechanism of action:

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 hepatocellular carcinoma and renal cell carcinoma, differentiated thyroid carcinoma and several other human tumour xenografts in immunocompromised mice.

5.2 Pharmacokinetic properties

Absorption and distribution:

After administration of sorafenib tablets, the mean relative bioavailability is 38 - 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 - 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 vivo* 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 concentrations of sorafenib administered at 400 mg twice daily were evaluated in thyroid carcinoma, 35 RCC and HCC patients. 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.

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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:

Croscarmellose sodium

Hypromellose

Magnesium stearate

Cellulose, microcrystalline

Silica, colloidal anhydrous

Sodium laurilsulfate

Talc

Tablet coating:

Hypromellose

Macrogol 3350

Titanium dioxide

Iron oxide red

6.2 Incompatibilities

Not applicable

6.3 Shelf life

24 months

6.4 Special precautions for storage

Store at or below 25 °C.

Keep blisters in the outer carton until required for use.

This medicine does not require any special storage conditions.

6.5 Nature and contents of container

Blister packs

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

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

This medicine could have potential risk for the environment. Any unused medicine or waste material should be disposed of in accordance with local requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Dr. Reddy's Laboratories (Pty) Ltd.

Block B, 204 Rivonia Road

Morningside

Sandton

2057

South Africa

8. REGISTRATION NUMBER(S)

56/26/1136

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of registration: 08 October 2024

10 DATE OF REVISION OF TEXT

Not applicable.