1.3.1.1 Proposed Professional Information

SCHEDULING STATUS

S4

1 NAME OF THE MEDICINE

EUROSTIB 200 mg Film-coated tablet

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 200 mg of sorafenib (as tosylate).

Sugar free.

For full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet.

Red-brown, round, biconvex film-coated tablets, debossed with “200” on one side and plain on the other side.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

EUROSTIB 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

The recommended daily dose of EUROSTIB is 400 mg (or 2 x 200 mg tablets) taken twice daily, 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.

Posology adjustments (dose titration, dose adjustment and 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 EUROSTIB therapy. When dose reduction is necessary during treatment of hepatocellular carcinoma (HCC) and advanced renal carcinoma (RCC), the EUROSTIB dose should be reduced to 400 mg daily.

Suggested dose modifications for skin toxicity with HCC and RCC:

Grade	**Occurrence**	**EUROSTIB dose modification**
Grade 1 (mild)	Any	Institute supportive measures immediately and continue EUROSTIB treatment.
Grade 2 (moderate)	First	Institute supportive measures immediately and consider a decrease EUROSTIB dose to 400 mg daily for 28 days • If toxicity returns to grade 0 to 1 after dose reduction, increase EUROSTIB to full dose after 28 days If toxicity does not return to grade 0 to 1 despite dose reduction, interrupt EUROSTIB treatment for a minimum of 7 days, until toxicity has resolved to grade 0 to 1 • When resuming treatment after dose interruption, resume EUROSTIB at reduced dose of 400 mg daily for 28 days • If toxicity is maintained at grade 0 to 1 at reduced dose, increase EUROSTIB to full dose after 28 days
	Second or Third	As for first occurrence, but upon resuming EUROSTIB treatment, decrease dose to 400 mg daily indefinitely
	Fourth	Discontinue EUROSTIB treatment
Grade 3 (severe)	First	Institute supportive measures immediately and interrupt EUROSTIB treatment for a minimum of 7 days and until toxicity has resolved to grade 0 to 1 • When resuming treatment after dose interruption, resume EUROSTIB at reduced dose of 400 mg daily for 28 days

		• If toxicity is maintained at grade 0 to 1 at reduced dose, increase EUROSTIB to full dose after 28 days
	Second	As for first occurrence, but upon resuming EUROSTIB treatment, decrease dose to 400 mg daily indefinitely
	Third	Discontinue EUROSTIB treatment.

Dose Reduction for Differentiated Thyroid Carcinoma:

Management of suspected side-effects may require temporary interruption and/or dose reduction of EUROSTIB therapy. When dose reduction is necessary during the treatment of differentiated thyroid carcinoma, the EUROSTIB 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, EUROSTIB 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 population

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

Elderly (above 65 years), gender and body weight

No dose adjustment is required on the basis if 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. EUROSTIB 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. EUROSTIB 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

- Hypersensitivity to sorafenib or to any of the excipients listed 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. Rash and hand foot skin reaction are usually CTC (Common Toxicity Criteria) Grade 1 and 2 and generally appear during the first six weeks of treatment with sorafenib. Management of dermatological toxicities may include topical therapies for symptomatic relief, temporary treatment interruption and/or dose modification of sorafenib, or in severe or persistent cases, permanent discontinuation of sorafenib (see section 4.8).

Hypertension

An increased incidence of arterial hypertension was observed in sorafenib-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 should be considered (see section 4.8).

Aneurysms and artery dissections

The use of Vascular endothelial growth factor (VEGF) pathway inhibitors in patients with or without hypertension may promote the formation of aneurysms and/or artery dissections. Before initiating EUROSTIB, 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 hospitalisation due to loss of consciousness, have been reported during sorafenib treatment. In case of symptomatic

hypoglycaemia, sorafenib should be temporarily interrupted. Blood glucose levels in diabetic patients should be checked regularly in order to assess if anti-diabetic medicine's dosage needs to be adjusted.

Haemorrhage

An increased risk of bleeding may occur following sorafenib administration. If any bleeding event necessitates medical intervention it is recommended that permanent discontinuation of EUROSTIB should be considered (see section 4.8).

Cardiac ischaemia and/or infarction

In a 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 another 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 EUROSTIB should be considered in patients who develop cardiac ischaemia and/or infarction (see section 4.8).

QT interval prolongation

Sorafenib has been shown to prolong the QT/QTc interval, which may lead to an increased risk for ventricular dysrhythmias. Use EUROSTIB 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 EUROSTIB 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. In some cases this was not associated with apparent intra-abdominal tumour. EUROSTIB 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 sections 4.2 and 5.2).

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 on wound healing have been conducted. Temporary interruption of EUROSTIB 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 EUROSTIB 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.

Interactions

Caution is recommended when administering sorafenib with compounds that are metabolised/eliminated predominantly by the UDP-glucuronosyltransferase 1 family, polypeptide A1 (UGT1A1) (e.g. irinotecan) or UGT1A9 pathways (see section 4.5).

Caution is recommended when sorafenib 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.

Higher mortality has been reported in patients with squamous cell carcinoma of the lung treated

with sorafenib in combination with platinum-based chemotherapies. In two randomised trials investigating patients with Non-Small Cell Lung Cancer in the subgroup of patients with squamous cell carcinoma treated with sorafenib as add-on to paclitaxel/carboplatin, the HR for overall survival was found to be 1.81 (95 % CI 1,19; 2,74) and as add-on to gemcitabine/cisplatin 1,22 (95 % CI 0,82; 1,80). No single cause of death dominated, but higher incidence of respiratory failure, haemorrhages and infectious adverse events were observed in patients treated with sorafenib as add-on to platinum-based chemotherapies.

Disease specific warnings

Differentiated thyroid cancer (DTC)

Before initiating treatment, medical practitioners 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 were 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 localised therapy prior to administering sorafenib in patients with DTC.

Hypocalcaemia in DTC

When using sorafenib in patients with DTC, close monitoring of blood calcium level is recommended. In clinical trials, hypocalcaemia was more frequent and more severe in patients with DTC, especially with a history of hypoparathyroidism, compared to patients with renal cell or hepatocellular carcinoma. Hypocalcaemia grade 3 and 4 occurred in 6,8 % and 3,4 % of sorafenib-treated patients with DTC (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 a study, increases in TSH levels above 0,5 mU/L were observed in sorafenib treated patients. When using EUROSTIB in DTC patients, close monitoring of TSH level is recommended.

Renal cell carcinoma

High Risk Patients, according to MSKCC (Memorial Sloan Kettering Cancer Centre) 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

EUROSTIB contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially "sodium free".

4.5 Interactions 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, phenobarbitone, 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 may be 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 sorafenib and midazolam, dextromethorphan or omeprazole, which are substrates for cytochromes CYP3A4, CYP2D6 and CYP2C19 respectively, did not alter the exposure of these medicines. This indicates that sorafenib 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.

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 ($\leq$ 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 with a 3-day break in sorafenib 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 are 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 is co-administered with docetaxel (see section 4.4).

Combination with other medicines

Neomycin

Co-administration of neomycin, a non-systemic antimicrobial medicine used to eradicate gastrointestinal flora, interferes with the enterohepatic recycling of sorafenib (see section 5.2, Biotransformation 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 %. 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 / Contraception in males and females

Women should avoid becoming pregnant while on therapy with EUROSTIB. 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). Adequate contraception should be used during therapy and for at least 2 weeks after completion of therapy.

Pregnancy

EUROSTIB should not be used during pregnancy. There are no data on the use of sorafenib in pregnant women. Studies in animals have shown reproductive toxicity including malformations. In rats, sorafenib and its metabolites were demonstrated to cross the placenta and sorafenib is anticipated to cause harmful effects to the foetus.

Lactation

It is not known whether sorafenib is excreted in human milk. In animals, sorafenib and/or its metabolites were excreted in milk. Because sorafenib could harm infant growth and development, women must not breastfeed during EUROSTIB treatment.

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.

No studies on the effects of the ability to drive and use machines have been performed.

It is not always possible to predict to what extent EUROSTIB may interfere with the daily activities of a patient.

Patients should ensure that they do not engage in the above activities until they are aware of the measure to which EUROSTIB affects them.

4.8 Undesirable effects

a. Summary of the safety profile

The most important serious adverse reactions were myocardial infarction/ischaemia, gastrointestinal perforation, medicine 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.

b. Tabulated summary of adverse reactions

SYSTEM ORGAN CLASS	**FREQUENCY**	**ADVERSE REACTIONS**
Infections and infestations	Frequent	Infection, folliculitis.
Blood and lymphatic system disorders	Frequent	Anaemia, leucopoenia, lymphopenia, neutropenia, thrombocytopenia.
Immune system disorders	Less frequent	Anaphylactic reaction, angioedema, hypersensitivity reactions (including skin reactions and urticaria).
Endocrine disorders	Frequent	Hypothyroidism.
	Less frequent	Hyperthyroidism.
Metabolism and nutrition disorders	Frequent	Anorexia, hypocalcaemia, hypoglycaemia, hypokalaemia, hyponatraemia, hypophosphataemia.
	Less frequent	Dehydration.
Psychiatric	Frequent	Depression.

disorders		
Nervous system disorders	Frequent	Dysgeusia, peripheral sensory neuropathy.
	Less frequent	Reversible posterior leukoencephalopathy. *
	Frequency unknown	Encephalopathy. #
Ear and labyrinth disorders	Frequent	Tinnitus.
Cardiac disorders	Frequent	Congestive heart failure, myocardial ischaemia and infarction. *
	Less frequent	QT prolongation.
Vascular disorders	Frequent	Flushing, haemorrhage (including gastrointestinal*, respiratory tract* and cerebral haemorrhage*), hypertension.
	Less frequent	Hypertensive crisis. *
	Frequency unknown	Aneurysms and artery dissections.
Respiratory, thoracic and mediastinal disorders	Frequent	Dysphonia, rhinorrhoea.
	Less frequent	Interstitial lung disease-like events* (pneumonitis, radiation pneumonitis, acute respiratory distress, etc.)
Gastrointestinal disorders	Frequent	Constipation, diarrhoea, dyspepsia, dysphagia, gastro-oesophageal reflux disease (GORD), nausea, vomiting, stomatitis (including dry mouth and glossodynia).
	Less frequent	Gastritis, gastrointestinal perforations*, pancreatitis.
Hepatobiliary disorders	Less frequent	cholangitis, cholecystitis, medicine induced hepatitis*, increase in bilirubin and jaundice.
Skin and subcutaneous	Frequent	Acne, alopecia, dermatitis exfoliative, dry skin, erythema, hand foot skin reaction **, hyperkeratosis,

tissue disorders		keratoacanthoma/squamous cell cancer of the skin, pruritis, rash, skin desquamation.
	Less frequent	Eczema, erythema multiforme, leucocytoclastic vasculitis, radiation recall dermatitis, Steven-Johnson syndrome, toxic epidermal necrolysis *.
Musculoskeletal and connective tissue disorders	Frequent	arthralgia, muscle spasms, myalgia.
	Less frequent	Rhabdomyolysis.
Renal and urinary disorders	Frequent	Proteinuria, renal failure.
	Less frequent	Nephrotic syndrome.
Reproductive system and breast disorders	Frequent	Erectile dysfunction.
	Less frequent	Gynaecomastia
General disorders and administration site conditions	Frequent	Asthenia, fatigue, fever, pain (including mouth, abdominal, bone, tumour pain and headache), influenza like illness, mucosal inflammation.
Investigations	Frequent	increased amylase, increased lipase, transient increase in transaminases, weight decreased.
	Less frequent	INR abnormal, prothrombin level abnormal, transient increase in blood alkaline phosphatase.

* The adverse reactions may have a life-threatening or fatal outcome. Such events are either uncommon or less frequent than uncommon.

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

Cases have been reported in the post marketing setting.

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 compared to patients in the renal cell or hepatocellular carcinoma studies.

d. Paediatric population

No information.

e. Other special population(s)

No information.

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 to SAHPRA via the "6.04 Adverse Drug Reaction Reporting Form", found online under SAHPRA's publications:

https://www.sahpra.org.za/Publications/Index/8

4.9 Overdose

There is no specific treatment for EUROSTIB overdose. The highest dose of sorafenib studied clinically is 800 mg twice daily. The adverse events observed at this dose were primarily diarrhoea and dermatological events. In the event of suspected overdose, EUROSTIB should be withheld and supportive care instituted where necessary.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacological classification: A 26 – Cytostatic Agents

ATC code: L01XE05

Sorafenib is a multikinase inhibitor which has demonstrated both anti-proliferative and anti-angiogenic properties *in vitro* and *in vivo*.

Mechanism of action and pharmacodynamic effects

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, VEGRF-3, and PDGFR-β). 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.

5.2 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.

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

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 tumour types. The clinical relevance of the increased AUC in thyroid carcinoma patients is unknown. Steady state plasma sorafenib AUQ (0-12)ss from differentiate 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]	39,36 (45 %) [10,69 to 103,9]	44,98 (52 %) [9,94 to 242,0]

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 CYP286 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

CYP1 A2 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.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core

Croscarmellose sodium

Hypromellose HPMC 2910

Magnesium stearate (E470b)

Microcrystalline cellulose (E460)

Sodium laurilsulfate

Film-coat

Hypromellose HPMC 2910

Titanium dioxide (E171)

Macrogol (E1521)

Red iron oxide (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months.

Store at or below 25 °C.

6.4 Special precautions for storage

No information.

6.5 Nature and contents of container

60’s film-coated tablets packed in Aluminium-OPA/Alu/PVC or in Aluminium-PVC/PE/PVDC blisters.The blisters are further packed in an outer carton box. Not all pack sizes may be marketed.

6.6 Special precautions for disposal

EUROSTIB 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

Eurolab (Pty) Ltd.

Woodmead Office Park,

3 Stirrup Lane

Van Reenens Avenue

Woodmead

2144

8 REGISTRATION NUMBER(S)

Unregistered medicine: To be allocated

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10 DATE OF REVISION OF THE TEXT