**Package Insert**

## 1. NAME OF THE MEDICINAL PRODUCT

Sorafenib Alvogen 200 mg film-coated tablets

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

For the full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Film-coated tablet (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

Hepatocellular carcinoma

Sorafenib is indicated for the treatment of patients with unresectable hepatocellular carcinoma (HCC) (see section 5.1).

Renal cell carcinoma

Sorafenib is indicated for the treatment of patients with advanced renal cell carcinoma who have failed prior systemic therapy or are considered unsuitable for such therapy.

Differentiated thyroid carcinoma

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

### 4.2 Posology and method of administration

Sorafenib treatment should be supervised by a physician experienced in the use of anticancer therapies.

Posology

*Recommended dose*
The recommended daily dose of sorafenib is 400 mg (2 x 200 mg tablets) taken twice a day, either without food or together with a 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 benefiting 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 drug reactions may require temporary interruption and/or dose reduction of sorafenib therapy. When dose reduction is necessary during the treatment of hepatocellular carcinoma (HCC) and advanced renal cell carcinoma (RCC), , the sorafenib dose should be reduced to two tablets of 200 mg once daily (see section 4.4).

Dose Reduction for Differentiated Thyroid Carcinoma
Management of suspected adverse drug reactions may require temporary interruption and/or dose reduction of sorafenib therapy.
When dose reduction is necessary during the treatment of differentiated thyroid carcinoma, the sorafenib dose should be reduced to 600mg daily in divided doses (two tablets of 200mg and one tablet of 200mg twelve hours apart).
If additional dose reduction is necessary, sorafenib may be reduced to one tablet of 200mg twice daily, followed by one tablet of 200mg once daily. After improvement of non-hematological adverse reactions, the dose of sorafenib may be increased.

| **Suggested Dose Reduction Levels for Patients with Differentiated Thyroid Carcinoma** | | |
|---|---|---|
| Dose Level | Sorafenib Dose | |
| 0 | 800mg daily dose | 400mg twice daily (2 tablets twice daily) |
| -1 | 600mg daily dose | 400mg and 200mg 12 hours apart (2 tablets and 1 tablet 12 hours apart – either dose can come first) |
| -2 | 400mg daily dose | 200mg twice daily (1 tablet twice daily) |
| -3 | 200mg daily dose | 200mg once daily (1 tablet once daily) |

| **Suggested Dose Modifications for Skin Toxicity in Patients with Differentiated Thyroid Carcinoma** | | |
|---|---|---|
| Grade | Occurrence | Sorafenib dose modification* |
| Grade 1: Numbness, dysesthesia, paresthesia, tingling, painless swelling, erythema or discomfort of the hands or feet which does not disrupt the patient's normal activities | Any | Institute supportive measures immediately and continue sorafenib treatment |
| Grade 2:<br>Painful erythema and swelling of the hands or feet and/or discomfort affecting the patient's normal activities | First | Institute supportive measures immediately and consider a decrease sorafenib dose to 600mg daily (400mg and 200mg 12 hours apart) If no improvement within 7 days, see below |
| | No improvement within 7 days or second occurrence | Interrupt sorafenib until resolved to grade 0-1. When sorafenib is resumed, decrease dose by one dose level |
| | Third | Interrupt sorafenib until resolved to grade 0-1. When |

| | | |
|---|---|---|
| | | sorafenib is resumed, decrease dose by two dose levels |
| | Fourth | Discontinue sorafenib permanently |
| Grade 3:<br>Moist desquamation, ulceration, blistering, or severe pain of the hands or feet, resulting in inability to work or perform activities of daily living | First | Interrupt sorafenib until resolved to grade 0-1. When sorafenib is resumed, decrease dose by one dose level |
| | Second | Interrupt sorafenib until resolved to grade 0-1. When sorafenib is resumed, decrease dose by two dose levels |
| | Third | Discontinue sorafenib permanently |

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

*Paediatric population*
The safety and efficacy of sorafenib in children and adolescents aged < 18 years have not yet been established. No data are available.

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

*Renal impairment*
No dose adjustment is required in patients with mild, moderate, or severe renal impairment not requiring dialysis. Sorafenib has not been studied in patients undergoing dialysis (see section 5.2).

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

*Hepatic impairment*
No dose adjustment is required in patients with Child Pugh A or B (mild to moderate) hepatic impairment. No data is available on patients with Child Pugh C (severe) hepatic impairment (see sections 4.4 and 5.2).

Method of administration

For oral use.
It is recommended that sorafenib should be administered without food or with a low or moderate fat meal. If the patient intends to have a high-fat meal, sorafenib tablets should be taken at least 1 hour before or 2 hours after the meal. The tablets should be swallowed with a glass of water.

## 4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

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

Hypoglycaemia

When using sorafenib 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 Undesirable effects). Severe hypocalcaemia should be corrected to prevent complications such as QT-prolongation or torsade de pointes (see section QT interval prolongation).

TSH Suppression in Differentiated Thyroid Carcinoma (DTC)

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

Thrombotic microangiopathy
Cases have been identified during post-approval use of sorafenib. 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.

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 sorafenib should be considered (see section 4.8). Due to the potential risk of bleeding, tracheal, bronchial, and esophageal infiltration should be treated with localized therapy prior to administering sorafenib in patients with differentiated thyroid carcinoma.

Cardiac ischaemia and/or infarction

In a randomised, placebo-controlled, double-blind study (study 1, see section 5.1) 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 study 3 (see section 5.1) 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 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 (see section 5.1), which may lead to an increased risk for ventricular arrhythmias. Use sorafenib with caution in patients who have, or may develop prolongation of QTc, such as patients with a congenital long QT syndrome, patients treated with a high cumulative dose of anthracycline therapy, patients taking certain anti-arrhythmic medicines or other medicinal products that lead to QT prolongation, and those with electrolyte disturbances such as hypokalaemia, hypocalcaemia, or hypomagnesaemia. When using sorafenib 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. Sorafenib 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 sorafenib 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 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.

Drug-drug interactions

Caution is recommended when administering sorafenib 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 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, hemorrhages and infectious adverse events were observed in patients treated with sorafenib as add-on to platinum-based chemotherapies.

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 medicinal products and other forms of interaction

UGT1A pathway

Caution is recommended when administering sorafenib together with compounds that are metabolized/eliminated predominantly by the UGT1A1 pathway (e.g. irinotecan) (see "Interactions with Other Medicinal Products and Other Forms of Interaction").

Docetaxel

Concomitant use of docetaxel (75 or 100 mg/m2) with sorafenib (200 or 400 mg twice daily), administered with a 3-day break in dosing around administration of docetaxel, resulted in a 36-80% increase in docetaxel AUC. Caution is recommended when sorafenib is co-administered with docetaxel (see "Interactions with Other Medicinal Products and Other Forms of Interaction").

Neomycin

Co-administration of neomycin may cause a decrease in sorafenib bioavailability (see "Interactions With Other Medicinal Products and Other Forms of Interaction").

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 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.

CYP2C9 substrates

The possible effect of sorafenib on warfarin, a CYP2C9 substrate, was assessed in sorafenib-treated patients compared to placebo-treated patients. The concomitant treatment with sorafenib and warfarin did not result in changes in mean PT-INR compared to placebo. However, patients taking warfarin should have their INR checked regularly (see section 4.4).

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 sorafenib administration did not alter the exposure of these agents. This indicates that sorafenib 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 pharmacokinetic study, concomitant administration of sorafenib 400 mg twice daily with cyclophosphamide, a CYP2B6 substrate, did not result in a clinically meaningful inhibition.

Combination with other anti-neoplastic agents

In clinical studies, sorafenib 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. 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 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 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 is co-administered with docetaxel (see section 4.4).

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 section 5.2), 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-administered of omeprazole has no impact on the pharmacokinetics of sorafenib. No dose adjustment for sorafenib is necessary.

## 4.6 Fertility, pregnancy and lactation

Pregnancy

There are no adequate and well-controlled studies in pregnant women using sorafenib. Studies in animals have shown reproductive toxicity including malformations (see "Special Warnings and Precautions for Use"). In rats, sorafenib and its metabolites were demonstrated to cross the placenta and sorafenib is anticipated to inhibit angiogenesis in the foetus.
Women should avoid becoming pregnant while on therapy. Women of childbearing potential must be apprised of the potential hazard to the foetus, which includes severe malformation (teratogenicity), failure to thrive and fetal death (embryotoxicity). Sorafenib should not be used during pregnancy. Prescribers may only consider it to be used, if the potential benefits justify the potential risks 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 (see section 5.3), women must not breast-feed during sorafenib treatment.

Fertility

Results from animal studies further indicate that sorafenib can impair male and female fertility (see section 5.3).

## 4.7 Effects on ability to drive and use machines

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

## 4.8 Undesirable effects

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

*Renal Cell Carcinoma*

**Table A: Adverse Reactions reported in at Least 5% of Patients in Any Treatment Group – Study 11213 in renal cell carcinoma (see study 11213).**

| | Sorafenib 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** | | | | | | |
| Arthralgia | 6 | <1 | 0 | 3 | 0 | 0 |
| Pain in extremity | 6 | <1 | 0 | 3 | 0 | 0 |
| **General Disorders and Administration Site Conditions** | | | | | | |
| Fatigue | 15 | 2 | 0 | 12 | <1 | 0 |
| Asthenia | 9 | <1 | 0 | 4 | <1 | 0 |

*Hepatocellular carcinoma*

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

| | | Sorafenib N= 297 | | | Placebo N= 302 | | |
|---|---|---|---|---|---|---|---|
| **System organ class** | **Preferred term** | **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** | **diarrhoea** | 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 % |

*Differentiated Thyroid Carcinoma*

**Table C: Adverse drug reactions (>10%) reported in patients treated with sorafenib and more commonly than in patients receiving placebo. (differentiated thyroid carcinoma study, double blind period, safety analysis set, CTCAE version 3.0)**

| **Adverse Event Category/term** | **Sorafenib (n=207)** | | | **Placebo (n=209)** | | |
|---|---|---|---|---|---|---|
| | **All Grades %** | **Grade 3 %** | **Grade 4 %** | **All Grades %** | **Grade 3 %** | **Grade 4 %** |
| **Cardiac general** | | | | | | |
| Hypertension | 41 | 10 | 0 | 12 | 2 | 0 |
| **Constitutional symptoms** | | | | | | |
| Fatigue | 50 | 5 | <1 | 25 | 1 | 0 |
| Weight Loss | 47 | 6 | 0 | 14 | 1 | 0 |
| Fever | 11 | 1 | <1 | 5 | 0 | 0 |
| **Dermatology/skin** | | | | | | |
| HFSR | 76 | 20 | 0 | 10 | 0 | 0 |
| Alopecia | 67 | 0 | 0 | 8 | 0 | 0 |
| Rash/Desquamation | 50 | 5 | 0 | 11 | 0 | 0 |
| Pruritus | 21 | 1 | 0 | 11 | 0 | 0 |
| Dry skin | 14 | <1 | 0 | 6 | 0 | 0 |
| **Gastrointestinal** | | | | | | |
| Diarrhea | 69 | 5 | <1 | 15 | 1 | 0 |
| Anorexia | 32 | 2 | 0 | 5 | 0 | 0 |
| Mucositis, oral cavity | 23 | <1 | <1 | 3 | 0 | 0 |
| Nausea | 21 | 0 | 0 | 11 | 0 | 0 |
| Constipation | 15 | 0 | 0 | 8 | <1 | 0 |
| Vomiting | 11 | <1 | 0 | 6 | 0 | 0 |
| **Infection** | | | | | | |

| | | | | | | |
|---|---|---|---|---|---|---|
| Infection (all) | 32 | 4 | 0 | 19 | 2 | 0 |
| **Pain** | | | | | | |
| Pain, head/headache | 18 | 0 | 0 | 7 | 0 | 0 |
| Pain, extremity-limb | 14 | <1 | 0 | 9 | <1 | 0 |
| Pain, abdomen | 14 | 1 | 0 | 4 | <1 | 0 |
| Pain, other | 11 | <1 | 0 | 8 | <1 | 0 |
| Pain, throat/pharynx/larynx | 10 | 0 | 0 | 4 | 0 | 0 |
| **Metabolic/Laboratory** | | | | | | |
| Hypocalcemia | 19 | 6 | 3 | 5 | <1 | 1 |
| ALT increased | 13 | 2 | <1 | 4 | 0 | 0 |
| AST increased | 11 | 1 | 0 | 2 | 0 | 0 |
| **Neuropathy** | | | | | | |
| Sensory neuropathy | 14 | 1 | 0 | 6 | 0 | 0 |
| **Pulmonary/upper respiratory** | | | | | | |
| Voice changes | 12 | <1 | 0 | 3 | 0 | 0 |

Adverse reactions reported in multiple clinical trials or through post-marketing use are listed below in Table 1, by system organ class (in MedDRA) and frequency. Frequencies are defined as: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), not known (cannot be estimated from the available data).

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

**Table 1: All adverse reactions reported in patients in multiple clinical trials or through post-marketing use**

| System organ class | Very common | Common | Uncommon | Rare | Not known |
|---|---|---|---|---|---|
| Infections and infestations | Infection | foliculitis | | | |
| Blood and lymphatic system disorders | lymphopenia | leucopenia<br>neutropenia<br>anaemia<br>thrombocytope-nia | | | Thrombotic microangiopathy |
| Immune system disorders | | | hypersensitivity reactions (including skin reactions and urticaria)<br>anaphylactic reaction | | angioedema |
| Endocrine disorders | | hypothyroidism | hyperthyroidism | | |
| Metabolism and nutrition disorders | anorexia<br>hypo-phosphataemia | hypocalcaemia<br>hypokalaemia<br>hyponatraemia | dehydratation | | |
| Psychiatric disorders | | depression | | | |
| Nervous system disorders | | peripheral sensory neuropathy<br>dysgeusia | reversible posterior leukoencephalo-pathy* | | |
| Ear and labyrinth disorders | | tinnitus | | | |
| Cardiac disorders | | congestive heart failure*<br>myocardial ischaemia and infarction* | | QT prolongation | |
| Vascular disorders | haemorrhage (inc. gastrointestinal*, respiratory tract* and cerebral haemorrhage*)<br>hypertension | flushing | hypertensive crisis* | | |
| Respiratory, thoracic and mediastinal disorders | | rhinorrhoea<br>dysphonia | interstitial lung disease-like events* | | dyspnea |
| Gastro-intestinal disorders | diarrhoea<br>nausea<br>vomiting<br>constipation | stomatitis (including dry mouth and glossodynia)<br>dyspepsia<br>dysphagia<br>gastro oesophageal reflux disease | pancreatitis<br>gastritis<br>gastrointestinal perforations* | | |
| Hepatobi-liary disorders | | | increase in bilirubin and jaundice, cholecystitis, cholangitis | drug induced hepatitis* | |

| | | | | | |
|---|---|---|---|---|---|
| Skin and subcutaneous tissue disorders | dry skin<br>rash<br>alopecia<br>hand foot skin reaction**<br>erythema<br>pruritus | keratoacan-thoma/ squamous cell cancer of the skin<br>dermatitis exfoliative<br>acne<br>skin desquamation<br>hyperkeratosis | eczema<br>erythema multiforme | | radiation recall dermatitis,<br><br>Stevens-Johnson syndrome,<br><br>leucocyto-clastic vasculitis,<br><br>toxic epidermal necrolysis* |
| Musculo-skeletal and connective tissue disorders | arthralgia | myalgia<br>muscle spasms | | | rhabdomyolysis |
| Renal and urinary disorders | | renal failure<br>proteinuria | | nephrotic syndrome | |
| Reproductive system and breast disorders | | erectile dysfunction | gynaecomastia | | |
| General disorders and adminis-tration site conditions | fatigue<br>pain (including mouth, abdominal, bone, tumour pain and headache)<br>fever | asthenia<br>influenza like illness<br>mucosal inflammation | | | |
| Investigations | weight decreased<br>increased amylase<br>increased lipase | transient increase in transaminases | transient increase in blood alkaline phosphatase<br><br>INR abnormal, prothrombin level abnormal | | |

* 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.

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 patients 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.

Two randomized 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 first-line treatment for patients with advanced Non-Small Cell Lung Carcinoma (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 compared to patients in the renal cell or hepatocellular carcinoma studies.

*Laboratory test abnormalities in RCC patients (study 11213)*
Elevated lipase and amylase levels were very commonly reported. In Study 11213, CTCAE grade 3 or 4 lipase elevations occurred in 12% of patients in the sorafenib group compared to 7% of patients in the placebo group. CTCAE grade 3 or 4 amylase elevations were reported in 1% of patients in the sorafenib group compared to 3% of patients in the placebo group. Clinical pancreatitis was reported in 2 of 451 sorafenib treated patients (CTCAE grade 4) and 1 of 451 patients (CTCAE grade 2) in the placebo group in Study 1.

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% on 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 etiology of hypophosphataemia associated with sorafenib is not known.

Hypocalcaemia was reported in 12% of sorafenib treated patients compared to 7.5% of placebo patients. Most reports of hypocalcaemia were low grade (CTCAE Grade 1 and 2). CTCAE grade 3 Hypocalcaemia (6.0 – 7.0 mg /dL) occurred in 1.1% of sorafenib treated patients and 0.2% of patients in the placebo group, and CTCAE grade 4 Hypocalcaemia (< 6.0 mg/dL) occurred in 1.1% of sorafenib treated patients and 0.5% of patients in the placebo group. The etiology of hypocalcaemia associated with sorafenib is not known.

Hypokalemia was reported in 5.4% of sorafenib treated patients compared to 0.7% of placebo patients. Most reports of hypokalemia were low grade (CTCAE Grade 1). CTCAE grade 3 Hypokalemia occurred in 1.3% of sorafenib treated patients and 0.2% of patients in the placebo group. There were no reports of grade 4 Hypokalemia.

*Laboratory abnormalities in HCC patients (study 100554):*
Elevated lipase was observed in 40% of patients treated with sorafenib 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 sorafenib 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, sorafenib treatment was not interrupted. Clinical pancreatitis was reported in 1 of 297 sorafenib-treated patients (CTCAE Grade 2).

Hypophosphatemia was a common laboratory finding, observed in 35% of sorafenib-treated patients compared to 11% of placebo patients; CTCAE Grade 3 hypophosphatemia (1–2 mg/dL) occurred in 11% of sorafenib-treated patients and 2% of patients in the placebo group; there was 1 case of CTCAE Grade 4 hypophosphatemia (<1 mg/dL) reported in the placebo group. The etiology of hypophosphatemia associated with sorafenib is not known.

Elevations in liver function tests were comparable between the 2 arms of the study. Elevated AST was observed in 94% of sorafenib-treated patients and 91% of placebo patients; CTCAE Grade 3 or 4 AST

elevations were reported in 16% of sorafenib-treated patients and 17% of patients in the placebo group. ALT elevations were observed in 69% of sorafenib-treated patients and 68% of placebo patients; CTCAE Grade 3 or 4 ALT elevations were reported in 3% of sorafenib-treated patients and 8% of placebo treated patients. Elevated bilirubin was observed in 47% of sorafenib-treated patients and 45% of placebo patients; CTCAE Grade 3 or 4 bilirubin elevations were reported in 10% of sorafenib-treated patients and 11% of placebo treated patients. Hypoalbuminemia was observed in 59% of sorafenib-treated patients and 47% of placebo patients; no CTCAE Grade 3 or 4 hypoalbuminemia was observed in either group.

Alkaline Phosphatase elevations were observed in 82.2% of sorafenib-treated patients and 82.5% of placebo patients; CTCAE Grade 3 Alkaline Phosphatase elevations were reported in 6.2% of sorafenib-treated patients and 8.2% of placebo treated patients; no CTCAE Grade 4 Alkaline Phosphatase elevation was observed in either group.

Thrombocytopenia was observed in 46% of sorafenib-treated patients and 41% of placebo patients; CTCAE Grade 3 or 4 thrombocytopenia was reported in 4% of sorafenib-treated patients and less than 1% of placebo patients.
Hypocalcaemia was reported in 26.5% of sorafenib treated patients compared to 14.8% of placebo patients. Most reports of hypocalcaemia were low grade (CTCAE Grade 1 and 2). CTCAE grade 3

Hypocalcaemia (6.0 – 7.0 mg /dL) occurred in 1.8% of sorafenib treated patients and 1.1% of patients in the placebo group, and CTCAE grade 4 Hypocalcaemia (< 6.0 mg/dL) occurred in 0.4% of sorafenib treated patients and 0% of patients in the placebo group. The etiology of hypocalcaemia associated with sorafenib is not known.
Hypokalemia was reported in 9.4% of sorafenib treated patients compared to 5.9% of placebo patients. Most reports of hypokalemia were low grade (CTCAE Grade 1). CTCAE grade 3

Hypokalemia occurred in 0.3% of sorafenib treated patients and 0.7% of patients in the placebo group. There were no reports of grade 4 Hypokalemia.

*Laboratory test abnormalities in thyroid carcinoma patients*
Hypocalcaemia was reported in 35.7% of sorafenib treated patients compared to 11.0% of placebo patients. 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.

Other clinically relevant laboratory abnormalities observed in the study 5 are shown in Table 2.

**Table 2: Treatment-emergent laboratory test abnormalities reported in DTC patient (study 5) double blind period**

| Laboratory parameter, (in % of samples investigated) | Sorafenib N = 207 | | | Placebo= N= 209 | | |
|---|---|---|---|---|---|---|
| | All Grades* | Grade 3* | Grade 4* | All Grades*. | Grade 3* | Grade 4* |
| Blood and lymphatic system disorders | | | | | | |
| Anemia | 30.9 | 0.5 | 0 | 23.4 | 0.5 | 0 |
| Thrombocytopenia | 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 disorder | | | | | | |
| Hypokalemia | 17.9 | 1.9 | 0 | 2.4 | 0 | 0 |
| Hypophosphatemia** | 19.3 | 12.6 | 0 | 2.4 | 1.4 | 0 |
| Hepatobiliary disorders | | | | | | |
| Bilirubin increased | 8.7 | 0 | 0 | 4.8 | 0 | 0 |

| | | | | | | |
|---|---|---|---|---|---|---|
| ALT increased | 58.9 | 3.4 | 1.0 | 24.4 | 0 | 0 |
| AST increased | 53.6 | 1.0 | 1.0 | 14.8 | 0 | 0 |
| Investigations | | | | | | |
| Amylase increased | 12.6 | 2.4 | 1.4 | 6.2 | 0 | 1.0 |
| Lipase increased | 11.1 | 2.4 | 0 | 2.9 | 0.5 | 0 |

* Common Terminology Criteria for Adverse Events (CTCAE), version 3.0
** The aetiology of hypophosphatemia associated with sorafenib is not known.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system.

### 4.9 Overdose

There is no specific treatment for sorafenib 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 sorafenib should be withheld and supportive care instituted where necessary.

## 5. PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic agents, protein kinase inhibitors, ATC code: L01EX02.

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, VEGFR- 2, VEGFR- 3, and PDGFR- ß). Several of these kinases are thought to be involved in tumour cell signaling, angiogenesis and apoptosis. Sorafenib inhibited tumour growth of the human hepatocellular carcinoma, renal cell carcinoma, differentiated thyroid carcinoma and several other human tumour xenografts in immunocompromised mice. A reduction in tumour angiogenesis were seen in models of human hepatocellular carcinoma and renal cell carcinoma and increases in tumour apoptosis wereseen in models of human hepatocellular, renal cell carcinoma and differentiated thyroid carcinoma. Additionally, a reduction in tumour cell signaling was seen in a model of human hepatocellular carcinoma and differentiated thyroid carcinoma.

Clinical efficacy

The clinical safety and efficacy of sorafenib 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 3 (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 sorafenib and placebo groups with regard to age, gender, race, performance status, etiology (including hepatitis B, hepatitis C and alcoholic liver disease), TNM 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 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 sorafenib 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 17hemoembolization; 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 sorafenib over placebo for OS (HR: 0.69, p= 0.00058, see Table 3). This advantage was consistent across almost all subsets analysed. In the prespecified stratification factors (ECOG status, presence or absence of macroscopic vascular invasion and/or extrahepatic tumour spread, and region) the hazard ratio consistently favoured sorafenib over placebo. The time to tumour progression (TTP, by independent radiological review) was significantly larger in the sorafenib Arm (HR: 0.58, p=0.000007 see Table 3).

**Table 3: Efficacy results from study 3 (study 100554) in hepatocellular carcinoma**

| Efficacy Parameter | Sorafenib (N=299) | Placebo (N=303) | P-value | HR (95% CI) |
|---|---|---|---|---|
| Overall Survival (OS) [median, weeks (95% CI)] | 46.3 (40.9, 57.9) | 34.4 (29.4, 39.4) | 0.00058* | 0.69 (0.55, 0.87) |
| Time to Progression (TTP) [median, weeks (95% CI)]** | 24.0 (18.0, 30.0) | 12.3 (11.7, 17.1) | 0.000007 | 0.58 (0.45, 0.74) |

CI=Confidence interval, HR=Hazard ratio (sorafenib over placebo)
* statistically significant as the p-value was below the prespecified O'Brien Fleming stopping boundary of 0.0077
** independent radiological review

Renal cell carcinoma

The safety and efficacy of sorafenib in the treatment of advanced renal cell carcinoma (RCC) were investigated in two clinical studies:

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

The TARGET study (Study 11213) was a Phase III, international, multi-centre, randomised, double blind, placebo-controlled study in 903 patients with advanced renal cell carcinoma who had received prior systemic therapy. Primary study endpoints included overall survival and progression-free survival (PFS). Tumour response rate was a secondary endpoint.

Patients were randomised to sorafenib 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, there was an estimated 39% improvement in overall survival for patients receiving sorafenib vs placebo. The estimated hazard ratio (risk of death with sorafenib 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 November 30, 2005, 367 deaths were reported, comprising 68% of the protocol-

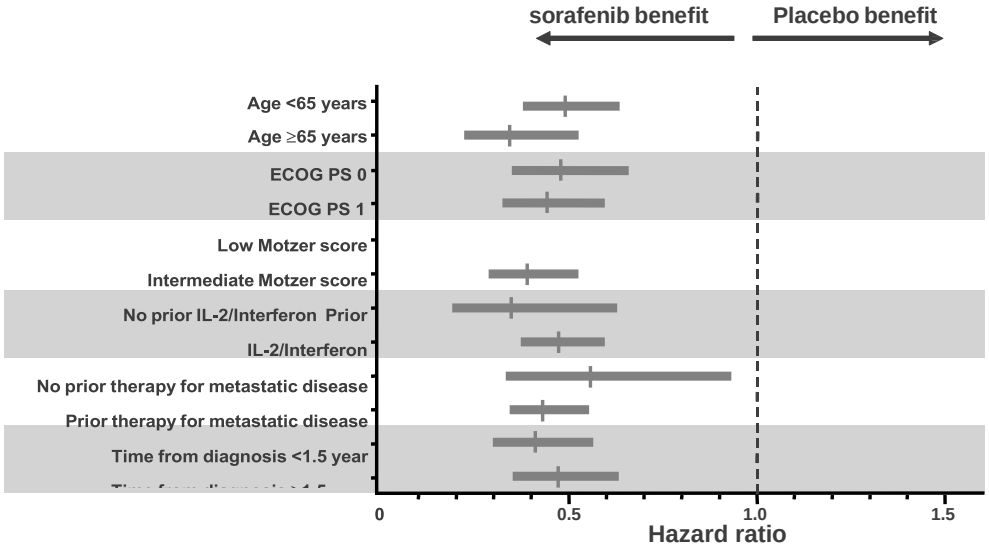
specified 540 survival events, there was an estimated 30% improvement in overall survival for patients receiving sorafenib compared to placebo. A total of 216 placebo patients had crossed over to sorafenib treatment. The median overall survival for the sorafenib and placebo group was 19.3 months and 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).

The PFS analysis included 769 patients randomised to sorafenib 400 mg twice daily (N=384) or to placebo (N=385). PFS was evaluated by blinded independent radiological review using RECIST criteria. The median PFS was double for patients randomised to sorafenib (167 days) compared to placebo patients (84 days), representing a 56% reduction in risk of progression for patients receiving sorafenib compared to placebo. (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 1. The effect of sorafenib 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 sorafenib compared to 85 days on placebo.

**Figure 1: Progression-Free Survival in Patient Subgroups (Hazard Ratio and 95% Cl for sorafenib : Placebo)**




Best overall tumour response was determined by investigator radiological review according to RECIST criteria. In the sorafenib 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 complete response, 8 patients (1.8%) had a partial response, and 239 patients (52.9%) had stable disease.

Overall, 293 patients in the sorafenib group and 281 patients in the placebo group had at least one post-baseline radiographic tumour evaluation available for independent review; tumour shrinkage was reported in 74% of patients receiving sorafenib compared to 20% of patients in the placebo group.

Sorafenib demonstrated no overall deterioration in kidney-cancer specific symptoms (FKSI-10) or health-related quality of life compared to placebo. At 18 and 24 weeks of treatment, more patients receiving sorafenib reported improvement in total FKSI-10 score (55 and 44%, respectively) and the physical well-being (FACT-G PWB) score (57 and 47%, respectively) versus placebo (FKSI-10, 33 and 21% and FACT-G PWB 37 and 21%, respectively).

Study 100391

Study 100391 was a Phase II randomised discontinuation trial in patients with metastatic malignancies, including RCC. The primary endpoint of the study was the percentage of randomised

patients (N=65) remaining progression-free at 24 weeks. Progression-free survival was significantly longer in the sorafenib 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 sorafenib (50%) than in the placebo patients (18%) (p=0.0077).

Differentiated thyroid carcinoma (DTC)

Study 4 was a Phase III, international, multi-centre, randomised, double blind, placebo-controlled trial in 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), tumor response rate and duration of response. Following progression, patients were allowed to receive open label sorafenib. Concomitant radioactive iodine treatment was not permitted.
Patients were included in the study if they experienced progression within 14 months of enrollment and had DTC refractory to 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 a 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. 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 sorafenib 400 mg twice daily and 210 patients randomised to placebo. PFS was evaluated by blinded independent radiological review using RECIST criteria.
Median PFS time was 329 days (10.8 months) in the sorafenib group compared to 175 days (5.8 months) in the placebo group. The relative risk for PFS (disease progression or death) was reduced by approximately 41% in sorafenib-treated patients compared to placebo-treated subjects with a hazard ratio. Hazard Ratio (HR) =0.587; 95% Confidence Interval (CI): 0.454, 0.758; one-sided p <0.0001). (Table 4)
The effect of sorafenib on PFS was consistent across all subsets including geographic region, age above or below 60 years, gender, histological subtype, tumor 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 4). 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 sorafenib received open-label sorafenib.
No complete response (CR) according to RECIST were observed. The overall response rate (CR + partial response (PR) per independent radiological assessment was higher in the sorafenib 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 sorafenib treated patients who experienced a PR.

**Table 4: Efficacy Results from Study 4 in Differentiated Thyroid Carcinoma**

| Efficacy Parameter | sorafenib (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 (sorafenib over placebo) *independent radiological review

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 msec and QTcF by 9 ±18 msec, as compared to placebo treatment at baseline. No subject showed a QTcB or QTcF >500 msec during the post-treatment ECG monitoring (see section 4.4).

## 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. The absolute bioavailability is not known. Following oral administration sorafenib reaches peak plasma concentrations in approximately 3 hours. When given with a high-fat meal sorafenib absorption was reduced by 30 % compared to administration in the fasted state.
Mean $C_{max}$ and AUC increased less than proportionally beyond doses of 400 mg administered twice daily. *In vitro* binding of sorafenib to human plasma proteins is 99.5 %.
Multiple dosing of sorafenib for 7 days resulted 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 DTC, RCC and HCC patients. The highest mean concentration was observed in DTC patients (approximately twice that observed in patients with RCC and HCC), though variability was high for all tumour types. The reason for the increased concentration in DTC patients is unknown.

Biotransformation and elimination

The elimination half-life of sorafenib is approximately 25 - 48 hours. Sorafenib is metabolised primarily in the liver and undergoes oxidative metabolism, mediated by CYP 3A4, as well as glucuronidation mediated by UGT1A9. Sorafenib conjugates may be cleaved in the gastrointestinal tract by bacterial glucuronidase activity, allowing reabsorption of unconjugated active substance. Co-administration of neomycin has been shown to interfere 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. This metabolite 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, indicating that biliary excretion of unchanged active substance might contribute to the elimination of sorafenib.

Pharmacokinetics in special population

Analyses of demographic data suggest that there is no relationship between pharmacokinetics and age (up to 65 years), gender or body weight.

Paediatric population

No studies have been conducted to investigate the pharmacokinetics of sorafenib in paediatric patients.

Race

There are no clinically relevant differences in pharmacokinetics between Caucasian and Asian subjects.

Renal impairment

In four Phase I clinical trials, steady state exposure to sorafenib was similar in patients with mild or moderate renal impairment compared to the exposures in patients with normal renal function. In a clinical pharmacology study (single dose of 400 mg sorafenib), no relationship was observed between sorafenib exposure and renal function in subjects with normal renal function, mild, moderate or severe renal impairment. No data is available in patients requiring dialysis.

Hepatic impairment

In hepatocellular carcinoma *(HCC)* patients with Child-Pugh A or B (mild to moderate) hepatic impairment, exposure values were comparable and within the range observed in patients without hepatic impairment. The pharmacokinetics (PK) of sorafenib in Child-Pugh A and B non-HCC patients were similar to the PK in healthy volunteers. There are no data for patients with Child-Pugh C (severe) hepatic impairment. Sorafenib is mainly eliminated via the liver, and exposure might be increased in this patient population.

## 5.3 Preclinical safety data

The preclinical safety profile of sorafenib was assessed in mice, rats, dogs and rabbits.
Repeat-dose toxicity studies revealed changes (degenerations and regenerations) in various organs at exposures below the anticipated clinical exposure (based on AUC comparisons).

After repeated dosing to young and growing dogs, effects on bone and teeth were observed at exposures below the clinical exposure. Changes consisted in irregular thickening of the femoral growth plate, hypocellularity of the bone marrow next to the altered growth plate and alterations of the dentin composition. Similar effects were not induced in adult dogs.

The standard program of genotoxicity studies was conducted and positive results were obtained as an increase in structural chromosomal aberrations in an *in vitro* mammalian cell assay (Chinese hamster ovary) for clastogenicity in the presence of metabolic activation was seen. Sorafenib was not genotoxic in the Ames test or in the *in vivo* mouse micronucleus assay. One intermediate in the manufacturing process, which is also present in the final active substance (< 0.15 %), was positive for mutagenesis in an *in vitro* bacterial cell assay (Ames test). Furthermore, the sorafenib batch tested in the standard genotoxicity battery included 0.34 % PAPE.
Carcinogenicity studies have not been conducted with sorafenib.

No specific studies with sorafenib have been conducted in animals to evaluate the effect on fertility. An adverse effect on male and female fertility can however be expected because repeat-dose studies in animals have shown changes in male and female reproductive organs at exposures below the anticipated clinical exposure (based on AUC). Typical changes consisted of signs of degeneration and retardation in testes, epididymides, prostate, and seminal vesicles of rats. Female rats showed central necrosis of the corpora lutea and arrested follicular development in the ovaries. Dogs showed tubular degeneration in the testes and oligospermia.

Sorafenib has been shown to be embryotoxic and teratogenic when administered to rats and rabbits at exposures below the clinical exposure. Observed effects included decreases in maternal and foetal body weights, an increased number of foetal resorptions and an increased number of external and visceral malformations.

Environmental Risk assessment studies have shown that sorafenib tosylate has the potential to be persistent, bioaccumulative and toxic to the environment.

## 6. PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

Tablet core:
Croscarmellose sodium
Cellulose, microcrystalline
Hypromellose
Sodium laurilsulfate
Magnesium stearate

Tablet coating:
Hypromellose
Macrogol
Titanium dioxide
Red iron oxide

### 6.2 Incompatibilities

Not applicable.

### 6.3 Shelf life

Please refer to packaging.

### 6.4 Special precautions for storage

Please refer to packaging.

### 6.5 Nature and contents of container

60 film-coated tablets (6 blisters x 10 tablets) or 112 film-coated tablets (4 blisters x 28 tablets) in Aluminium-OPA/Alu/PVC blisters or in Aluminium-PVC/PE/PVDC blisters.

Not all pack sizes may be marketed.

### 6.6 Special precautions for disposal

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

## 7. PRODUCT OWNER

LOTUS INTERNATIONAL PTE. LTD.
80 Robinson Road
#02-00
Singapore 068898

## 8. DATE OF REVISION OF THE TEXT

01/2023