# SUMMARY OF PRODUCT CHARACTERISTICS

## 1. NAME OF THE MEDICINAL PRODUCT

Sorafenib betapharm 200 mg, filmomhulde tabletten

## 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, which are debossed with “200” on one side and plain on the other side with a diameter of tablet of 12.0 mm ± 5%.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

Hepatocellular carcinoma
Sorafenib betapharm is indicated for the treatment of hepatocellular carcinoma (see section 5.1).

Renal cell carcinoma
Sorafenib betapharm is indicated for the treatment of patients with advanced renal cell carcinoma who have failed prior interferon-alpha or interleukin-2 based therapy or are considered unsuitable for such therapy.

Differentiated thyroid carcinoma
<Product name> is indicated for the treatment of patients with progressive, locally advanced or metastatic, differentiated (papillary/follicular/Hürthle cell) thyroid carcinoma, refractory to radioactive iodine.

### 4.2 Posology and method of administration

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

Posology
The recommended dose of Sorafenib betapharm in adults is 400 mg sorafenib (two tablets of 200 mg) twice daily (equivalent to a total daily dose of 800 mg).

Treatment should continue as long as clinical benefit is observed or until unacceptable toxicity occurs.

Posology adjustments
Management of suspected adverse drug reactions may require temporary interruption 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 betapharm dose should be reduced to two tablets of 200 mg sorafenib once daily (see section 4.4).

When dose reduction is necessary during the treatment of differentiated thyroid carcinoma (DTC), the <Product name> dose should be reduced to 600 mg sorafenib daily in divided doses (two tablets of 200 mg and one tablet of 200 mg twelve hours apart).
If additional dose reduction is necessary, <Product name> may be reduced to 400 mg sorafenib daily in divided doses (two tablets of 200 mg twelve hours apart), and, if necessary, further reduced to one tablet of 200 mg once daily. After improvement of non-haematological adverse reactions, the dose of <Product name> may be increased.

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

*Elderly population*
No dose adjustment is required in the elderly (patients above 65 years of age).

*Renal impairment*
No dose adjustment is required in patients with mild, moderate or severe renal impairment. No data is available in patients requiring 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
Decreases in blood glucose, in some cases clinically symptomatic and requiring hospitalization 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 medicinal product'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 sorafenib should be considered (see section 4.8).

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).

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

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, 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, physicians are recommended to carefully evaluate the prognosis in the individual patient considering maximum lesion size (see section 5.1), symptoms related to the disease (see section 5.1) and progression rate.

Management of suspected adverse drug reactions may require temporary interruption or dose reduction of sorafenib therapy. In study 5 (see section 5.1), 37% of subjects had dose interruption and 35% had dose reduction already in cycle 1 of sorafenib treatment.

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 localized 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 study 5 (see section 5.1), increases in TSH levels above 0.5 mU/L were observed in sorafenib treated patients. When using sorafenib in DTC patients, close monitoring of TSH level is recommended.

*Renal cell carcinoma*
High risk patients, according to MSKCC (Memorial Sloan Kettering Cancer Center) prognostic group, were not included in the phase III clinical study in renal cell carcinoma (see study 1 in section 5.1), and benefit-risk in these patients has not been evaluated.

Information about excipients
This medicine contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially "sodium-free".

**4.5 Interaction with other medicinal products and other forms of interaction**

Inducers of metabolic enzymes
Administration of rifampicin for 5 days before administration of a single dose of sorafenib resulted in an average 37% reduction of sorafenib AUC. Other inducers of CYP3A4 activity and/or glucuronidation (e.g. *Hypericum perforatum* also known as St. John's wort, phenytoin, carbamazepine, phenobarbital, and dexamethasone) may also increase metabolism of sorafenib and thus decrease sorafenib concentrations.

CYP3A4 inhibitors
Ketoconazole, a potent inhibitor of CYP3A4, administered once daily for 7 days to healthy male volunteers did not alter the mean AUC of a single 50 mg dose of sorafenib. These data suggest that clinical pharmacokinetic interactions of sorafenib with CYP3A4 inhibitors are unlikely.

CYP2B6, CYP2C8 and CYP2C9 substrates
Sorafenib inhibited CYP2B6, CYP2C8 and CYP2C9 *in vitro* with similar potency. However, in clinical pharmacokinetic studies, concomitant administration of sorafenib 400 mg twice daily with cyclophosphamide, a CYP2B6 substrate, or paclitaxel, a CYP2C8 substrate, did not result in a clinically meaningful inhibition. These data suggest that sorafenib at the recommended dose of 400 mg twice daily may not be an *in vivo* inhibitor of CYP2B6 or CYP2C8.
Additionally, concomitant treatment with sorafenib and warfarin, a CYP2C9 substrate, did not result in changes in mean PT-INR compared to placebo. Thus, also the risk for a clinically relevant *in vivo* inhibition of CYP2C9 by sorafenib 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 agents. 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 agents

In clinical studies sorafenib has been administered with a variety of other anti-neoplastic agents at their commonly used dosing regimens including gemcitabine, cisplatin, oxaliplatin, paclitaxel, carboplatin, capecitabine, doxorubicin, irinotecan, docetaxel and cyclophosphamide. Sorafenib had no clinically relevant effect on the pharmacokinetics of gemcitabine, cisplatin, carboplatin, oxaliplatin or cyclophosphamide.

Paclitaxel/carboplatin

- Administration of paclitaxel (225 mg/m$^2$) and carboplatin (AUC = 6) with sorafenib (≤ 400 mg twice daily), administered with a 3-day break in sorafenib dosing (two days prior to and on the day of paclitaxel/carboplatin administration), resulted in no significant effect on the pharmacokinetics of paclitaxel.
- Co-administration of paclitaxel (225 mg/m$^2$, once every 3 weeks) and carboplatin (AUC = 6) with sorafenib (400 mg twice daily, without a break in sorafenib dosing) resulted in a 47% increase in sorafenib exposure, a 29% increase in paclitaxel exposure and a 50% increase in 6-OH paclitaxel exposure. The pharmacokinetics of carboplatin were unaffected.

These data indicate no need for dose adjustments when paclitaxel and carboplatin are co-administered with sorafenib 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 (750–1,050 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 other agents

*Neomycin*

Co-administration of neomycin, a non-systemic antimicrobial agent used to eradicate gastrointestinal flora, interferes with the enterohepatic recycling of sorafenib (see section 5.2, Metabolism and Elimination), resulting in decreased sorafenib exposure. In healthy volunteers treated with a 5-day regimen of neomycin the average exposure to sorafenib decreased by 54%. 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

Pregnancy
There are no data on the use of sorafenib in pregnant women. Studies in animals have shown reproductive toxicity including malformations (see section 5.3). In rats, sorafenib and its metabolites were demonstrated to cross the placenta and sorafenib is anticipated to cause harmful effects on the foetus. Sorafenib should not be used during pregnancy unless clearly necessary, after careful consideration of the needs of the mother and the risk to the foetus.
Women of childbearing potential must use effective contraception during treatment.

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

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

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 ($\geq$ 1/10), common ($\geq$ 1/100 to < 1/10), uncommon ($\geq$ 1/1,000 to < 1/100), rare ($\geq$ 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 | folliculitis | | | |
| Blood and lymphatic system disorders | lymphopenia | leucopenia<br>neutropenia<br>anaemia<br>thrombocy-topenia | | | |

| System organ class | Very common | Common | Uncommon | Rare | Not known |
|---|---|---|---|---|---|
| Immune system disorders | | | hypersensitivity reactions (including skin reactions and urticaria) anaphylactic reaction | angioedema | |
| Endocrine disorders | | hypothyroid-ism | hyperthyroid-ism | | |
| Metabolism and nutrition disorders | anorexia hypophospha-taemia | hypocal-caemia hypokalaemia hyponatrae-mia hypoglycae-mia | dehydration | | tumour lysis syndrome |
| Psychiatric disorders | | depression | | | |
| Nervous system disorders | | peripheral sensory neuropathy dysgeusia | reversible posterior leukoencepha-lopathy* | | encephalopa-thy° |
| Ear and labyrinth disorders | | tinnitus | | | |
| Cardiac disorders | | congestive heart failure* myocardial ischaemia and infarction* | | QT prolongation | |
| Vascular disorders | haemorrhage (inc. gas-trointestinal*, respiratory tract* and cerebral haemor-rhage*) hypertension | flushing | hypertensive crisis* | | aneurysms and artery dissections |
| Respiratory, thoracic and mediastinal disorders | | rhinorrhoea dysphonia | interstitial lung disease-like events* (pneumonitis, radiation pneumonitis, acute respiratory distress, etc.) | | |

| System organ class | Very common | Common | Uncommon | Rare | Not known |
|---|---|---|---|---|---|
| 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* | | |
| Hepatobiliary 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 | keratoacanthoma/squamous cell cancer of the skin<br>dermatitis exfoliative<br>acne<br>skin desquamation<br>hyperkeratosis | eczema<br>erythema multiforme | radiation recall dermatitis<br>Stevens-Johnson syndrome<br>leucocytoclastic vasculitis<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 administration 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>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.

° Cases have been reported in the post marketing setting.

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 = 2,276). 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.

*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 HCC (study 3) and RCC (study 1) patients

Increased lipase and amylase were very commonly reported. CTCAE Grade 3 or 4 lipase elevations occurred in 11% and 9% of patients in the sorafenib group in study 1 (RCC) and study 3 (HCC), respectively, compared to 7% and 9% of patients in the placebo group. CTCAE Grade 3 or 4 amylase elevations were reported in 1% and 2% of patients in the sorafenib group in study 1 and study 3, respectively, compared to 3% of patients in each placebo group. Clinical pancreatitis was reported in 2 of 451 sorafenib treated patients (CTCAE Grade 4) in study 1, 1 of 297 sorafenib treated patients in study 3 (CTCAE Grade 2), and 1 of 451 patients (CTCAE Grade 2) in the placebo group in study 1.
Hypophosphataemia was a very common laboratory finding, observed in 45% and 35% of sorafenib treated patients compared to 12% and 11% of placebo patients in study 1 and study 3, respectively. CTCAE Grade 3 hypophosphataemia (1–2 mg/dl) in study 1 occurred in 13% of sorafenib treated patients and 3% of patients in the placebo group, in study 3 in 11% of sorafenib treated patients and 2% 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 in study 1, and 1 case in the placebo group in study 3. The aetiology of hypophosphataemia associated with sorafenib is not known.

CTCAE Grade 3 or 4 laboratory abnormalities occurring in ≥ 5% of sorafenib treated patients included lymphopenia and neutropenia.

Hypocalcaemia was reported in 12% and 26.5% of sorafenib treated patients compared to 7.5% and 14.8% of placebo patients in study 1 and study 3, respectively. 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% and 1.8% of sorafenib treated patients and 0.2% and 1.1% of patients in the placebo group, and CTCAE grade 4 hypocalcaemia (< 6.0 mg/dL) occurred in 1.1% and 0.4% of sorafenib treated patients and 0.5% and 0% of patients in the placebo group in study 1 and 3, respectively. The aetiology of hypocalcaemia associated with sorafenib is not known.

In studies 1 and 3 decreased potassium was observed in 5.4% and 9.5% of sorafenib-treated patients compared to 0.7% and 5.9% of placebo patients, respectively. Most reports of hypokalaemia were low grade (CTCAE Grade 1). In these studies CTCAE Grade 3 hypokalaemia occurred in 1.1% and 0.4% of sorafenib treated patients and 0.2% and 0.7% of patients in the placebo group. There were no reports of hypokalaemia CTCAE grade 4.

Laboratory test abnormalities in DTC patients (study 5)

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 | | | | | | |
| Anaemia | 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 disorders | | | | | | |
| Hypokalaemia | 17.9 | 1.9 | 0 | 2.4 | 0 | 0 |
| Hypophosphataemia** | 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 listed below.
Nederlands Bijwerkingen Centrum Lareb
Website: www.lareb.nl

### 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 inhibits tumour growth of a broad spectrum of human tumour xenografts in athymic mice accompanied by a reduction of tumour angiogenesis. Sorafenib inhibits the activity of targets present in the tumour cell (CRAF, BRAF, V600E BRAF, c-KIT, and FLT-3) and in the tumour vasculature (CRAF, VEGFR-2, VEGFR-3, and PDGFR-ß). RAF kinases are serine/threonine kinases, whereas c-KIT, FLT-3, VEGFR-2, VEGFR-3, and PDGFR-ß are receptor tyrosine kinases.

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 study in 602 patients with hepatocellular carcinoma. Demographics and baseline disease characteristics were comparable between the sorafenib and the placebo group with regard to ECOG status (status 0: 54% vs. 54%; status 1: 38% vs. 39%; status 2: 8% vs. 7%), 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%), and BCLC stage (stage B: 18.1% vs. 16.8%; stage C: 81.6% vs. 83.2%; stage D: < 1% vs. 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).

There are limited data from this study in patients with Child Pugh B liver impairment and only one patient with Child Pugh C had been included.

**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

A second Phase III, international, multi-centre, randomised, double blind, placebo-controlled study (Study 4, 11849) evaluated the clinical benefit of sorafenib in 226 patients with advanced hepatocellular carcinoma. This study, conducted in China, Korea and Taiwan confirmed the findings of Study 3 with respect to the favourable benefit-risk profile of sorafenib (HR [OS]: 0.68, p = 0.01414).

In the pre-specified stratification factors (ECOG status, presence or absence of macroscopic vascular invasion and/or extrahepatic tumour spread) of both Study 3 and 4, the HR consistently favoured sorafenib over placebo. Exploratory subgroup analyses suggested that patients with distant metastases at baseline derived a less pronounced treatment effect.

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 1 (study 11213) was a Phase III, multi-centre, randomised, double blind, placebo-controlled study in 903 patients. Only patients with clear cell renal carcinoma and low and intermediate risk MSKCC (Memorial Sloan Kettering Cancer Center) were included. The primary endpoints were overall survival and progression-free survival (PFS).
Approximately half of the patients had an ECOG performance status of 0, and half of the patients were in the low risk MSKCC prognostic group.
PFS was evaluated by blinded independent radiological review using RECIST criteria. The PFS analysis was conducted at 342 events in 769 patients. The median PFS was 167 days for patients randomised to sorafenib compared to 84 days for placebo patients (HR = 0.44; 95% CI: 0.35–0.55; $p < 0.000001$). Age, MSKCC prognostic group, ECOG PS and prior therapy did not affect the treatment effect size.

An interim analysis (second interim analysis) for overall survival was conducted at 367 deaths in 903 patients. The nominal alpha value for this analysis was 0.0094. The median survival was 19.3 months for patients randomised to sorafenib compared to 15.9 months for placebo patients (HR = 0.77; 95% CI: 0.63–0.95; $p = 0.015$). At the time of this analysis, about 200 patients had crossed-over to sorafenib from the placebo group.

Study 2 was a Phase II, discontinuation study in patients with metastatic malignancies, including RCC. Patients with stable disease on therapy with sorafenib were randomised to placebo or continued sorafenib therapy. Progression-free survival in patients with RCC was significantly longer in the sorafenib group (163 days) than in the placebo group (41 days) ($p = 0.0001$, HR = 0.29).

Differentiated thyroid carcinoma (DTC)
Study 5 (study 14295) was a Phase III, international, multi-centre, randomised, double blind, placebo-controlled trial in 417 patients with locally advanced or metastatic DTC refractory to radioactive iodine. Progression-free survival (PFS) as evaluated by a blinded independent radiological review using RECIST criteria was the primary endpoint of the study. Secondary endpoints included overall survival (OS), tumour response rate and duration of response. Following progression, patients were allowed to receive open label sorafenib.
Patients were included in the study if they experienced progression within 14 months of enrolment and had DTC refractory to radioactive iodine (RAI). DTC refractory to RAI was defined as having a lesion without iodine uptake on a RAI scan, or receiving cumulative RAI ≥ 22.2 GBq, or experiencing a progression after a RAI treatment within 16 months of enrolment 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. The median delivered cumulative radioactive iodine activity before enrolment was approximately 14.8 GBq. Majority of patients had papillary carcinoma (56.8%), followed by follicular (25.4%) and poorly differentiated carcinoma (9.6%).

Median PFS time was 10.8 months in the sorafenib group compared to 5.8 months in the placebo group (HR = 0.587; 95% Confidence Interval [CI]: 0.454, 0.758; one-sided $p < 0.0001$). The effect of sorafenib on PFS was consistent independent of geographic region, age above or below 60 years, gender, histological subtype, and presence or absence of bone metastasis.

In an overall survival analysis conducted 9 months after the data cut-off for the final PFS analysis there was no statically significant difference in overall survival between the treatment groups (HR = 0.884; 95% CI: 0.633, 1.236, one-sided p value of 0.236). The median OS was not reached in the sorafenib arm and was 36.5 months in the placebo arm. 175 (75%) patients randomised to placebo and 61 (30%) patients randomised to sorafenib received open-label sorafenib.

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

No complete response (CR) according to RECIST was observed. The overall response rate (CR + partial response [PR]) per independent radiological assessment was higher in the sorafenib group (24 patients, 12.2%) 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.

A post-hoc subgroup analysis by maximum tumour size showed a treatment effect for PFS in favour of sorafenib over placebo for patients with maximum tumour size of 1.5 cm or larger (HR 0.54 [95% CI: 0.41–0.71]) whereas a numerically lower effect was reported in patients with a maximum tumour size of less than 1.5 cm (HR 0.87 [95% CI: 0.40–1.89]).

A post-hoc subgroup analysis by thyroid carcinoma symptoms at baseline showed a treatment effect for PFS in favour of sorafenib over placebo for both symptomatic and asymptomatic patients. The HR of progression free survival was 0.39 (95% CI: 0.21–0.72) for patients with symptoms at baseline and 0.60 (95% CI: 0.45–0.81) for patients without symptoms at baseline.

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 $4 \pm 19$ msec and QTcF by $9 \pm 18$ 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).

Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies, in all subsets of the paediatric population, in kidney and renal pelvis carcinoma (excluding nephroblastoma, nephroblastomatosis, clear cell sarcoma, mesoblastic nephroma, renal medullary carcinoma and rhabdoid tumour of the kidney) and liver and intrahepatic bile duct carcinoma (excluding hepatoblastoma) and differentiated thyroid carcinoma (see section 4.2 for information on paediatric use).

## 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 populations
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.
In a 2-year mouse carcinogenicity study there were cases of colon adenocarcinoma associated with severe hyperplasia and inflammation, and in a 2-year rat carcinogenicity study there were cases of

pancreatic islet cell adenoma. Systemic exposures achieved in both carcinogenicity studies were below clinical exposures in humans at the recommended dose. The observed cases were few in numbers and the clinical relevance of these findings is unknown.

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. Environmental Risk Assessment information is available in the EPAR of this medicine (see section 6.6).

## 6. PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

Tablet core
Hypromellose (E464)
Croscarmellose sodium (E468)
Cellulose, microcrystalline (E460)
Magnesium stearate (E470b)
Sodium laurilsulfate (E514)

Tablet coating
Hypromellose (E464)
Titanium dioxide (E171)
Macrogol (E1521)
Red iron oxide (E172)

### 6.2 Incompatibilities

Not applicable.

### 6.3 Shelf life

4 years

### 6.4 Special precautions for storage

Do not store above 30 °C.

### 6.5 Nature and contents of container

112 film-coated tablets in Aluminium-PVC/PE/PVDC blisters or 112 x 1 film-coated tablet in Aluminium-PVC/PE/PVDC perforated unit dose 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. MARKETING AUTHORISATION HOLDER

betapharm Arzneimittel GmbH
Kobelweg 95
Augsburg 86156
Duitsland

## 8. MARKETING AUTHORISATION NUMBER(S)

RVG 126081

## 9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Datum van eerste verlening van de vergunning: 27 juni 2020
Datum van laatste verlenging: 2 juni 2025

## 10. DATE OF REVISION OF THE TEXT

Laatste gedeeltelijke wijziging betreft rubriek 5.3: 10 september 2025