

**SORAFENIB- sorafenib tablet, film coated**  
**Twi Pharmaceuticals, Inc.**

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**HIGHLIGHTS OF PRESCRIBING INFORMATION**

**These highlights do not include all the information needed to use SORAFENIB TABLETS safely and effectively.**

**See full prescribing information for SORAFENIB TABLETS.**

**Sorafenib tablets, for oral use**

**Initial U.S. Approval: 2005**

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**RECENT MAJOR CHANGES** -----

Warnings and Precautions, Risk of Impaired Wound Healing (5.7) 5/2020

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**INDICATIONS AND USAGE** -----

Sorafenib tablets are a kinase inhibitor indicated for the treatment of

- Unresectable hepatocellular carcinoma(1.1)
- Locally recurrent or metastatic, progressive, differentiated thyroid carcinoma (DTC) refractory to radioactive iodine treatment (1.3)

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**DOSAGE AND ADMINISTRATION** -----

• *The recommended dosage is 400 mg orally twice daily without food. (2.1)*

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**DOSAGE FORMS AND STRENGTHS** -----

Tablets: 200 mg (3)

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**CONTRAINDICATIONS** -----

- Sorafenib tablets are contraindicated in patients with known severe hypersensitivity to sorafenib or any other component of sorafenib tablets. (4)
- Sorafenib tablets in combination with carboplatin and paclitaxel is contraindicated in patients with squamous cell lung cancer. (4)

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- Sorafenib tablets in combination with carboplatin and paclitaxel is contraindicated in patients with squamous cell lung cancer. (4)

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**WARNINGS AND PRECAUTIONS** -----

- **Cardiovascular Events:** Consider temporary or permanent discontinuation of sorafenib tablets.(2.2, 5.1)
- **Hemorrhage:** Discontinue sorafenib tablets if needed. (5.2)
- **Hypertension:** Monitor blood pressure weekly during the first 6 weeks and periodically thereafter. Consider temporary or permanent discontinuation for severe or persistent hypertension despite antihypertensive therapy.(5.3)
- **Dermatologic Toxicities:** Interrupt and/or decrease dose. Discontinue for severe or persistent reactions, or if Stevens-Johnson syndrome and toxic epidermal necrolysis is suspected.(5.4)
- **Gastrointestinal Perforation:** Discontinue sorafenib tablets. (5.5)
- **Risk of Impaired Wound Healing:** Withhold sorafenib tablets for at least 10 days prior to elective surgery. Do not administer for at least 2 weeks following major surgery and until adequate wound healing. The safety of resumption of sorafenib tablets after resolution of wound healing complications has not been established. (5.7)
- **QT Prolongation:** Monitor electrocardiograms and electrolytes in patients at increased risk for ventricular arrhythmias. Correct electrolytes. Interrupt if QTc greater than 500 msec or increases greater than 60 msec from baseline.( 2.2, 5.9, 12.2)
- **Drug-Induced Liver Injury:** Monitor liver function tests regularly; discontinue for unexplained transaminase elevations. (5.10)
- **Embryo-Fetal Toxicity:** Sorafenib tablets may cause fetal harm. Advise patients of the potential risk to a fetus and to use effective contraception. (5.11, 8.1, 8.3)
- **Impairment of Thyroid Stimulating Hormone Suppression (TSH) in DTC:** Monitor TSH monthly and adjust thyroid replacement therapy in patients with thyroid cancer. (5.12)

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**ADVERSE REACTIONS** -----

The most common adverse reactions ( $\geq 20\%$ ) are diarrhea, fatigue, infection, alopecia, hand-foot skin reaction, rash, weight loss, decreased appetite, nausea, gastrointestinal and abdominal pains, hypertension, and hemorrhage. (6)

**To report SUSPECTED ADVERSE REACTIONS, contact Twi Pharmaceuticals, Inc. at 1-844-518-2989 or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch)**

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**DRUG INTERACTIONS** -----

- Strong CYP3A Inducers: Avoid strong CYP3A4 inducers.(7.1)

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**USE IN SPECIFIC POPULATIONS** -----

- **Lactation:** Advise women not to breastfeed. (8.2)

**See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.**

**Revised: 5/2023**

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### **4 CONTRAINDICATIONS**

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## 1 INDICATIONS AND USAGE

### 1.1 Hepatocellular Carcinoma

Sorafenib tablets are indicated for the treatment of patients with unresectable hepatocellular carcinoma (HCC).

### 1.3 Differentiated Thyroid Carcinoma

Sorafenib tablets are indicated for the treatment of patients with locally recurrent or metastatic, progressive, differentiated thyroid carcinoma (DTC) that is refractory to radioactive iodine treatment.

## 2 DOSAGE AND ADMINISTRATION

### 2.1 Recommended Dosage

The recommended dosage of sorafenib tablets is 400 mg orally twice daily without food (at least 1 hour before or 2 hours after a meal) until the patient is no longer clinically benefiting from therapy or until unacceptable toxicity.

### 2.2 Dose Modifications for Adverse Reactions

#### Recommended Dosage Modifications

The recommended dosage modifications for adverse reactions are provided in Tables 1, 2, and 3.

**Table 1: Recommended Dose Reductions for Adverse Reactions**

	<b>Dose Reduction Hepatocellular Carcinoma</b>	<b>Differentiated Thyroid Carcinoma</b>
First Dose	400 mg orally once daily	400 mg orally in the morning and 200 mg orally in the evening about 12 hours apart
Reduction		OR 200 mg orally in the morning and 400 mg orally in the evening about 12 hours apart
Second Dose	200 mg orally once daily	OR 200 mg orally twice daily
Reduction	400 every other day	
Third Dose	None	200 mg orally once daily
Reduction		

*Table 2: Recommended Dosage Modifications of Sorafenib Tablets for Adverse Reactions*

<b>Adverse Reaction Severity<sup>1</sup></b>	<b>Sorafenib Tablets Dosage Modification</b>
<b>Cardiovascular Events</b> [see Warnings and Precautions (5.1)]	
Cardiac Ischemia and/or Infarction	Grade 2 and above Permanently discontinue.
Congestive Heart Failure	Grade 3 Interrupt <sup>2</sup> until Grade 1 or less, resume at reduced dose by 1 dose level. <sup>3</sup> Grade 4 Permanently discontinue.
<b>Hemorrhage</b> [see Warnings and Precautions (5.2)]	Grade 2 and above requiring medical intervention Permanently discontinue.
	Grade 2 (symptomatic/persistent) Interrupt until symptoms

	OR Grade 2 symptomatic increase by greater than 20 mm Hg (diastolic) or greater than 140/90 mm Hg if previously within normal limits	resolve and diastolic blood pressure less than 90 mm Hg, then resume at reduced dose by 1 dose level. <sup>3</sup> If needed, reduce another dose level. <sup>3</sup>
<b>Hypertension</b> [see Warnings and Precautions (5.3)]	OR Grade 3 Grade 4	Permanently discontinue.
<b>Gastrointestinal Perforation</b> [see Warnings and Precautions (5.5)]	Any grade	Permanently discontinue.
<b>QT Interval Prolongation</b> [see Warnings and Precautions (5.9)]	Greater than 500 milliseconds OR Increase from baseline of 60 milliseconds or greater	Interrupt and correct electrolyte abnormalities (magnesium, potassium, calcium). Use medical judgement before restarting.
<b>Drug-Induced Liver Injury</b> [see Warnings and Precautions (5.10)]	Grade 3 ALT or higher in the absence of another cause <sup>4</sup> OR AST/ALT greater than 3 × upper limit normal (ULN) with bilirubin greater than 2 × ULN in the absence of another cause <sup>4</sup>	Permanently discontinue.
	Grade 2 Grade 3	Continue treatment at reduced dose by 1 dose level.
	1 <sup>st</sup> occurrence	Interrupt until Grade 2 or less, then resume at reduced dose by 1 dose level.
<b>Non-hematological toxicities</b> [see Adverse Reactions (6.1)]	No improvement within 7 days OR 2 <sup>nd</sup> or 3 <sup>rd</sup> occurrence	Interrupt until Grade 2 or less, then resume at reduced dose by 2 dose levels.
	4 <sup>th</sup> occurrence	Interrupt until Grade 2 or less, then resume at reduced dose by 2 dose levels for HCC or 3 dose levels for DTC.
	Grade 4	Permanently discontinue.

1. Adverse reactions graded according to National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0 (NCI CTCAE v3.0).

2. If no recovery after 30 day interruption, discontinue treatment unless the patient is deriving clinical benefit.

3. If more than 2 dose reductions are required, permanently discontinue treatment.

4. In addition, any grade increased alkaline phosphatase in the absence of known bone pathology and Grade 2 or worse increased bilirubin; any 1 of the following: INR of 1.5 or greater, ascites and/or encephalopathy in the absence of underlying cirrhosis or other organ failure considered to be due to drug-induced liver injury.

Table 3: Recommended Dosage Modifications for Dermatologic Toxicities

Dermatologic Toxicity Grade	Occurrence	Sorafenib Tablets Dosage Modification	
		Hepatocellular	Differentiated Thyroid Carcinoma
Grade 2: Painful erythema and swelling of the hands or feet and/or	1 <sup>st</sup> occurrence	Continue sorafenib tablets and consider	Decrease sorafenib tablets to 600 mg daily If no improvement within 7

discomfort affecting the patient's normal activities

topical therapy days, see below.  
for symptomatic relief.  
If no improvement within 7 days, see below.

	No improvement within 7 days at reduced dose	Interrupt sorafenib tablets until resolved or improved to Grade 0 to 1.	Interrupt sorafenib tablets until completely resolved or improved to Grade 1.
	OR 2 <sup>nd</sup> and 3 <sup>rd</sup> occurrence	When resuming treatment, decrease dose by 1 dose level.	When resuming treatment, decrease dose by 1 dose level for 2 <sup>nd</sup> occurrence and 2 dose levels for 3 <sup>rd</sup> occurrence.
Grade 3: Moist desquamation, ulceration, blistering, or severe pain of the hands or feet, resulting in inability to work or perform activities of daily living	4 <sup>th</sup> occurrence	Discontinue sorafenib tablets treatment	
	1 <sup>st</sup> occurrence	Interrupt sorafenib tablets until resolved or improved to Grade 0 to 1	Interrupt sorafenib tablets until completely resolved or improved to Grade 1.
		When resuming treatment, decrease dose by 1 dose level.	When resuming treatment, decrease dose by 1 dose level.
	2 <sup>nd</sup> occurrence	Interrupt sorafenib tablets until resolved or improved to Grade 0 to 1	Interrupt sorafenib tablets until completely resolved or improved to Grade 1.
		When resuming treatment, decrease dose by 1 dose level.	When resuming treatment, decrease dose by 2 dose levels.
	3 <sup>rd</sup> occurrence	Discontinue sorafenib tablets treatment	

Following improvement of Grade 2 or 3 dermatologic toxicity to Grade 0 or 1 for at least 28 days on a reduced dose of sorafenib tablets, the dose of sorafenib tablets may be increased 1 dose level from the reduced dose. Approximately 50% of patients requiring a dose reduction for dermatologic toxicity are expected to meet these criteria for resumption of the higher dose and roughly 50% of patients resuming the previous dose are expected to tolerate the higher dose (that is, maintain the higher dose level without recurrent Grade 2 or higher dermatologic toxicity).

**3 DOSAGE FORMS AND STRENGTHS**

Sorafenib Tablets USP, 200 mg are round, pink, film-coated tablets, debossed with the "YB" on one side and "201" on the other side.

**4 CONTRAINDICATIONS**

- Sorafenib tablets are contraindicated in patients with known severe hypersensitivity to sorafenib or any other component of Sorafenib tablets.
- Sorafenib tablets in combination with carboplatin and paclitaxel are contraindicated in patients with squamous cell lung cancer [see Warnings and Precautions (5.8)].

**4 CONTRAINDICATIONS**

- Sorafenib tablets are contraindicated in patients with known severe hypersensitivity to sorafenib or any other component of Sorafenib tablets.
- Sorafenib tablets in combination with carboplatin and paclitaxel are contraindicated in patients with squamous cell lung cancer [see *Warnings and Precautions (5.8)*].

## 5 WARNINGS AND PRECAUTIONS

### 5.1 Cardiovascular Events

In the SHARP (HCC) study, the incidence of cardiac ischemia/infarction was 2.7% in sorafenib tablets-treated patients compared with 1.3% in those receiving placebo, and in the DECISION (DTC) study, the incidence of cardiac ischemia/infarction was 1.9% in the sorafenib tablets -treated group compared with 0% in patients receiving placebo. Patients with unstable coronary artery disease or recent myocardial infarction were excluded from this study. In multiple clinical trials, congestive heart failure has been reported in 1.9% of sorafenib tablets-treated patients (N=2276) [see *Adverse Reactions (6.2)*].

Consider temporary or permanent discontinuation of sorafenib tablets in patients who develop cardiovascular events [see *Dosage and Administration (2.2)*].

### 5.2 Hemorrhage

An increased risk of bleeding may occur following sorafenib tablets administration. In the SHARP (HCC) study, the rates of bleeding from esophageal varices (2.4% and 4%) and of bleeding with a fatal outcome from any site (2.4% and 4%) were similar in Sorafenib tablets -treated patients and those receiving placebo, respectively. In the DECISION (DTC) study, bleeding was reported in 17.4% of sorafenib tablets -treated patients and 9.6% of those receiving placebo; however, the incidence of Grade 3 bleeding was similar (1% and 1.4%) in sorafenib tablets -treated patients and in those receiving placebo.

If any bleeding necessitates medical intervention, consider permanent discontinuation of sorafenib tablets [see *Dosage and Administration (2.2)*]. Due to the potential risk of bleeding, treat tracheal, bronchial, and esophageal infiltration with local therapy prior to administering sorafenib tablets in patients with DTC.

### 5.3 Hypertension

In the SHARP (HCC) study, hypertension was reported in 9.4% of sorafenib tablets-treated patients and 4.3% of patients receiving placebo. In the DECISION (DTC) study, hypertension was reported in 40.6% of sorafenib tablets-treated patients and 12.4% of patients receiving placebo. Hypertension was usually mild to moderate, occurred early in the course of treatment, and was managed with standard antihypertensive therapy. Permanent discontinuation due to hypertension occurred in 1 of 297 sorafenib tablets-treated patients in the SHARP (HCC) study, and 1 of 207 sorafenib tablets -treated patients in the DECISION (DTC) study.

Monitor blood pressure weekly during the first 6 weeks of sorafenib tablets. Thereafter, monitor blood pressure and treat hypertension, if required, in accordance with standard medical practice. In cases of severe or persistent hypertension despite institution of antihypertensive therapy, consider temporary or permanent discontinuation of sorafenib tablets [see *Dosage and Administration (2.2)*].

### 5.4 Dermatologic Toxicities

Hand-foot skin reaction and rash represent the most common adverse reactions attributed to sorafenib tablets. Rash and hand-foot skin reaction are usually Grade 1 and 2 and generally appear during the first six weeks of treatment with sorafenib tablets. Permanent discontinuation of therapy due to hand-foot skin reaction occurred in 4 (1.3%) of 297 sorafenib tablets -treated patients with HCC, and 11 (5.3%) of 207 sorafenib tablets-treated patients with DTC.

Management of dermatologic toxicities may include topical therapies for symptomatic relief, temporary treatment interruption and/or dose reduction of sorafenib tablets, or in severe or persistent cases, permanent discontinuation of sorafenib tablets [see *Dosage*

and Administration (2.2)].

There have been reports of severe dermatologic toxicities, including Stevens- Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN). These cases may be life-threatening. Discontinue sorafenib tablets if SJS or TEN are suspected.

### **5.5 Gastrointestinal Perforation**

Gastrointestinal perforation has been reported in less than 1% of patients taking sorafenib tablets. In some cases this was not associated with apparent intra-abdominal tumor. In the event of a gastrointestinal perforation, permanently discontinue sorafenib tablets.

### **5.6 Increased Risk of Bleeding with Concomitant Use of Warfarin**

Infrequent bleeding or elevations in the International Normalized Ratio (INR) have been reported in some patients taking warfarin while on sorafenib tablets. Monitor patients taking concomitant warfarin regularly for changes in prothrombin time (PT), INR or clinical bleeding episodes.

### **5.7 Risk of Impaired Wound Healing**

Impaired wound healing can occur in patients who receive drugs that inhibit the VEGF signaling pathway. Therefore, sorafenib tablets has the potential to adversely affect wound healing.

Withhold sorafenib tablets for at least 10 days prior to elective surgery. Do not administer for at least 2 weeks following major surgery and until adequate wound healing. The safety of resumption of sorafenib tablets after resolution of wound healing complications has not been established.

### **5.8 Increased Mortality Observed with Sorafenib Tablets Administered in Combination with Carboplatin/Paclitaxel and Gemcitabine/Cisplatin in Squamous Cell Lung Cancer**

In a subset analysis of two randomized controlled trials in chemo-naïve patients with Stage IIIB-IV non-small cell lung cancer, patients with squamous cell carcinoma experienced higher mortality with the addition of sorafenib tablets compared to those treated with carboplatin/paclitaxel alone (HR 1.81; 95% CI 1.19, 2.74) and gemcitabine/cisplatin alone (HR 1.22; 95% CI 0.82, 1.80). The use of sorafenib tablets in combination with carboplatin/paclitaxel is contraindicated in patients with squamous cell lung cancer. Sorafenib tablets in combination with gemcitabine/cisplatin are not recommended in patients with squamous cell lung cancer. The safety and effectiveness of sorafenib tablets has not been established in patients with non-small cell lung cancer.

### **5.9 QT Interval Prolongation**

Sorafenib tablets can prolong the QT/QTc interval. QT/QTc interval prolongation increases the risk for ventricular arrhythmias.

Avoid sorafenib tablets in patients with congenital long QT syndrome. Monitor electrolytes and electrocardiograms in patients with congestive heart failure, bradyarrhythmias, drugs known to prolong the QT interval, including Class Ia and III antiarrhythmics. Correct electrolyte abnormalities (magnesium, potassium, calcium). Interrupt sorafenib tablets if QTc interval is greater than 500 milliseconds or for an increase from baseline of 60 milliseconds or greater [see *Clinical Pharmacology* (12.2)].

### **5.10 Drug-Induced Liver Injury**

Sorafenib-induced hepatitis is characterized by a hepatocellular pattern of liver damage with significant increases of transaminases which may result in hepatic failure and death. Increases in bilirubin and INR may also occur. The incidence of severe drug-induced liver injury, defined as elevated transaminase levels above 20 times the upper limit of normal or transaminase elevations with significant clinical sequelae (for example, elevated INR, ascites, fatal, or transplantation), was two of 3,357 patients (0.06%) in a global monotherapy database.

Monitor liver function tests regularly. In case of significantly increased transaminases without alternative explanation, such as viral hepatitis or progressing underlying malignancy, discontinue sorafenib tablets [see *Dosage and Administration (2.2)*].

### 5.11 Embryo-Fetal Toxicity

Based on its mechanism of action and findings in animals, sorafenib tablets may cause fetal harm when administered to a pregnant woman. Sorafenib caused embryo-fetal toxicities in animals at maternal exposures that were significantly lower than the human exposures at the recommended dose of 400 mg twice daily. Advise pregnant women and females of reproductive potential of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment and for 6 months following the last dose of sorafenib tablets. Advise male patients with female partners of reproductive potential and pregnant partners to use effective contraception during treatment and for 3 months following the last dose of sorafenib tablets [see *Use in Specific Populations (8.1, 8.3)*].

### 5.12 Impairment of Thyroid Stimulating Hormone Suppression in Differentiated Thyroid Carcinoma

Sorafenib tablets impairs exogenous thyroid suppression. In the DECISION (DTC) study, 99% of patients had a baseline thyroid stimulating hormone (TSH) level less than 0.5 mU/L. Elevation of TSH level above 0.5 mU/L was observed in 41% of sorafenib tablets - treated patients as compared with 16% of those receiving placebo patients. For patients with impaired TSH suppression while receiving sorafenib tablets, the median maximal TSH was 1.6 mU/L and 25% had TSH levels greater than 4.4 mU/L.

Monitor TSH levels monthly and adjust thyroid replacement medication as needed in patients with DTC.

## 6 ADVERSE REACTIONS

The following clinically significant adverse reactions are discussed elsewhere in the labeling:

- *Cardiovascular events [see Warnings and Precautions (5.1)]*
- *Hemorrhage [see Warnings and Precautions (5.2)]*
- *Hypertension [see Warnings and Precautions (5.3)]*
- *Dermatologic toxicities [see Warnings and Precautions (5.4)]*
- *Gastrointestinal perforation [see Warnings and Precautions (5.5)]*
- *QT interval prolongation [see Warnings and Precautions (5.9) and Clinical Pharmacology(12.2)]*
- *Drug-induced liver injury [see Warnings and Precautions (5.10)]*
- *Impairment of TSH suppression in DTC [see Warnings and Precautions (5.12)]*

### 6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The data described reflect exposure to sorafenib tablets in 504 patients who participated in placebo-controlled studies in hepatocellular carcinoma (N=297), or differentiated thyroid carcinoma (N = 207). The most common adverse reactions ( $\geq 20\%$ ), which were considered to be related to sorafenib tablets, in patients with HCC or DTC are diarrhea, fatigue, infection, alopecia, hand-foot skin reaction, rash, weight loss, decreased appetite, nausea, gastrointestinal and abdominal pains, hypertension, and hemorrhage.

#### Hepatocellular Carcinoma

Table 4 shows the percentage of patients in the SHARP (HCC) study experiencing adverse reactions that were reported in at least 10% of patients and at a higher rate in the Sorafenib Tablets -treated group than in those receiving placebo.

#### **Table 4: Adverse Reactions Reported in at Least 10% of Patients and at a Higher Rate in Sorafenib Tablets Arm than the Placebo Arm-SHARP (HCC)**



Adverse Reaction <sup>1</sup>	Sorafenib Tablets N = 297			Placebo N = 302		
	All Grades	Grade 3%	Grade 4%	All Grades %	Grade 3%	Grade 4%
<b>Any Adverse Reaction</b>	98	39	6	96	24	8
<b>Gastrointestinal</b>						
Diarrhea	55	10	< 1	25	2	0
Anorexia	29	3	0	18	3	< 1
Nausea	24	1	0	20	3	0
Vomiting	15	2	0	11	2	0
Constipation	14	0	0	10	0	0
<b>Constitutional symptoms</b>						
Fatigue	46	9	1	45	12	2
Weight loss	30	2	0	10	1	0
Pain						
Pain, abdomen	31	9	0	26	5	1
<b>Dermatology/skin</b>						
Hand-foot skin reaction	21	8	0	3	< 1	0
Rash/desquamation	19	1	0	14	0	0
Alopecia	14	0	0	2	0	0
Pruritus	14	< 1	0	11	< 1	0
Dry skin	10	0	0	6	0	0
<b>Hepatobiliary/pancreas</b>						
Liver dysfunction	11	2	1	8	2	1

1. Adverse reactions graded according to National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0 (NCI CTCAE v3.0).

Hypertension was reported in 9% of patients treated with sorafenib tablets and 4% of those receiving placebo. Grade 3 hypertension was reported in 4% of sorafenib tablets -treated patients and 1% of those receiving placebo.

Hemorrhage/bleeding was reported in 18% of those receiving sorafenib tablets and 20% of patients receiving placebo. The rates of Grade 3 and 4 bleeding were also higher in patients receiving placebo (Grade 3 - 3% sorafenib tablets and 5% placebo and Grade 4 - 2% sorafenib tablets and 4% placebo). Bleeding from esophageal varices was reported in 2.4% in sorafenib tablets -treated patients and 4% of patients receiving placebo.

Renal failure was reported in <1% of patients treated with sorafenib tablets and 3% of patients receiving placebo. Clinical pancreatitis was reported in 1 of 297 sorafenib tablets -treated patients (Grade 2).

The rate of adverse reactions (including those associated with progressive disease) resulting in permanent discontinuation was similar in both the sorafenib tablets -treated patients and those receiving placebo (32% of sorafenib tablets -treated patients and 35% of patients receiving placebo).

Laboratory test abnormalities reported in SHARP are presented in Table 5.

**Table 5: Laboratory Test Abnormalities Reported in SHARP (HCC)**

Laboratory Parameter <sup>1</sup>	Sorafenib Tablets N=297		Placebo N=302	
	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
Hypoalbuminemia	59	0	47	0
Elevated Lipase	40	9	37	9
Lymphopenia	47	NR	42	NR
Thrombocytopenia	46	4	41	1
Elevated INR	42	4	34	2

Hypophosphatemia <sup>35</sup>	11	11	2
Elevated Amylase	34	2	29
Hypocalcemia	27	2.4	15
Hypokalemia	10	□1	6
			□1

1. Laboratory parameters graded according to National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0 (NCI CTCAE v3.0).

NR = not reported

### Differentiated Thyroid Carcinoma

The safety of sorafenib tablets was evaluated in DECISION in 416 patients with locally recurrent or metastatic, progressive differentiated thyroid carcinoma (DTC) refractory to radioactive iodine (RAI) treatment randomized to receive 400 mg twice daily sorafenib tablets (n=207) or matching placebo (n=209) until disease progression or intolerable toxicity in a double-blind trial [see Clinical Studies (14.3)]. The data described below reflect a median exposure to sorafenib tablets for 46 weeks (range 0.3 to 135). The population exposed to sorafenib tablets was 50% male, and had a median age of 63 years.

Dose interruptions for adverse reactions were required in 66% of patients receiving sorafenib tablets and dose reductions were required in 64% of patients. Adverse reactions that resulted in treatment discontinuation were reported in 14% of sorafenib tablets -treated patients compared to 1.4% of patients receiving placebo.

Table 8 shows the percentage of DTC patients experiencing adverse reactions at a higher rate in sorafenib tablets -treated patients than in patients receiving placebo in the double-blind phase of the DECISION study. Grade 3 adverse reactions occurred in 53% of sorafenib tablets -treated patients compared to 23% of patients receiving placebo. Grade 4 adverse reactions occurred in 12% of sorafenib tablets-treated patients compared to 7% of patients receiving placebo.

**Table 8: Selected Adverse Reactions Occurring at a Higher Incidence in Sorafenib Tablets -Treated Patients [Between Arm Difference of 5% (All Grades )1 or 2% (Grades 3 and 4)]**

Adverse Reaction	Sorafenib Tablets N = 207		Placebo N = 209	
	All Grades (%)	Grades 3 and 4 (%)	All Grades (%)	Grades 3 and 4 (%)
<b>Skin and subcutaneous tissue disorders</b>				
PPES <sup>5</sup>	69	19	8	0
Alopecia	67	0	8	0
Rash	35	5	7	0
Pruritus	20	0.5	11	0
Dry skin	13	0.5	5	0
Erythema	10	0	0.5	0
Hyperkeratosis	7	0	0	0
<b>Gastrointestinal disorders</b>				
Diarrhea	68	6	15	1
Stomatitis <sup>3</sup>	24	2	3	0
Nausea	21	0	12	0
Abdominal pain <sup>2</sup>	20	1	7	1
Constipation	16	0	8	0.5
Oral pain <sup>4</sup>	14	0.5	6	0
Vomiting	11	0	3	0
<b>Investigations</b>				
Weight loss	49	6	14	1
<b>General disorders and administration site conditions</b>				
Fatigue	41	5	20	1
Asthenia	12	0	7	0

Pyrexia	11	1	5	0
<b>Vascular disorders</b>				
Hypertension <sup>6</sup>	41	10	12	2
<b>Metabolism and nutrition disorders</b>				
Decreased appetite	30	2	5	0
<b>Nervous system disorders</b>				
Headache	17	0	6	0
Dysgeusia	6	0	0	0
<b>Musculoskeletal and connective tissue disorders</b>				
Pain in extremity	15	1	7	0
Muscle spasms	10	0	3	0
<b>Respiratory, thoracic and mediastinal disorders</b>				
Dysphonia	13	0.5	3	0
Epistaxis	7	0	1	0
<b>Neoplasms benign, malignant and unspecified</b>				
Squamous cell carcinoma <sub>3</sub> of skin		3	0	0

1. National Cancer Institute Common Terminology Criteria for Adverse Events Version 3.0
2. Includes the following terms: abdominal pain, abdominal discomfort, hepatic pain, esophageal pain, esophageal discomfort, abdominal pain lower, abdominal pain upper, abdominal tenderness, abdominal rigidity
3. Includes the following terms: stomatitis, aphthous stomatitis, mouth ulceration, mucosal inflammation
4. Includes the following terms: oral pain, oropharyngeal discomfort, glossitis, burning mouth syndrome, glossodynia
5. Palmar-plantar erythrodysesthesia syndrome (Hand-foot skin reaction)
6. Includes the following terms: hypertension, blood pressure increased, blood pressure systolic increased

The relative increase for the following laboratory abnormalities observed in sorafenib tablets -treated patients as compared to patients receiving placebo in the DECISION study is similar to that observed in the HCC studies: lipase, amylase, hypokalemia, hypophosphatemia, neutropenia, lymphopenia, anemia, and thrombocytopenia. Hypocalcemia was more frequent and more severe in patients with DTC, especially those with a history of hypoparathyroidism, compared to patients with HCC. Other laboratory test abnormalities reported in DECISION are presented in Table 9.

**Table 9: Laboratory Test Abnormalities Reported in DECISION (DTC)**

Laboratory Parameter <sup>1</sup>	Sorafenib Tablets N=207		Placebo N=209	
	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
Elevated ALT	59	4	24	0
Elevated AST	54	2	15	0
Hypocalcemia	36	10	11	3

1 Laboratory parameters graded according to National Cancer Institute Common Terminology Criteria for adverse events version 3.0 (NCI CTCAE v3.0).

#### Additional Data from Multiple Clinical Trials

The following additional drug-related adverse reactions and laboratory abnormalities were reported from clinical trials of sorafenib tablets (very common 10% or greater, common 1 to less than 10%, uncommon 0.1% to less than 1%, rare less than 0.1 %):

Cardiovascular:*Common*: congestive heart failure\*<sup>†</sup>, myocardial ischemia and/or infarction *Uncommon*: hypertensive crisis\* *Rare*: QT prolongation\*

Dermatologic:*Very common*: erythema *Common*: exfoliative dermatitis, acne, flushing, folliculitis, hyperkeratosis *Uncommon*: eczema, erythema multiforme

**Digestive:***Very common:* increased lipase, increased amylase *Common:* mucositis, stomatitis (including dry mouth and glossodynia), dyspepsia, dysphagia, gastrointestinal reflux *Uncommon:* pancreatitis, gastritis, gastrointestinal perforations\*, cholecystitis, cholangitis

Note that elevations in lipase are very common (41%, see below); a diagnosis of pancreatitis should not be made solely on the basis of abnormal laboratory values

**General Disorders:***Very common:* infection, hemorrhage (including gastrointestinal\* and respiratory tract\* and uncommon cases of cerebral hemorrhage\*), asthenia, pain (including mouth, bone, and tumor pain), pyrexia, decreased appetite *Common:* influenza-like illness

**Hematologic:***Very common:* leukopenia, lymphopenia *Common:* anemia, neutropenia, thrombocytopenia *Uncommon:* INR abnormal

**Hepatobiliary disorders:***Rare:* drug-induced hepatitis (including hepatic failure and death)

**Hypersensitivity:***Uncommon:* hypersensitivity reactions (including skin reactions and urticaria), anaphylactic reaction

**Metabolic and Nutritional:***Very common:* hypophosphatemia *Common:* transient increases in transaminases, hypocalcemia, hypokalemia, hyponatremia, hypothyroidism *Uncommon:* dehydration, transient increases in alkaline phosphatase, increased bilirubin (including jaundice), hyperthyroidism

**Musculoskeletal:***Very common:* arthralgia *Common:* myalgia, muscle spasms

**Nervous System and Psychiatric:***Common:* depression, dysgeusia *Uncommon:* tinnitus, reversible posterior leukoencephalopathy\*

**Renal and Genitourinary:***Common:* renal failure, proteinuria *Rare:* nephrotic syndrome

**Reproductive:***Common:* erectile dysfunction *Uncommon:* gynecomastia

**Respiratory:***Common:* rhinorrhea *Uncommon:* interstitial lung disease-like events (includes reports of pneumonitis, radiation pneumonitis, acute respiratory distress, interstitial pneumonia, pulmonitis and lung inflammation)

In addition, the following medically significant adverse reactions were uncommon during clinical trials of sorafenib tablets: transient ischemic attack, arrhythmia, and thromboembolism. For these adverse reactions, the causal relationship to sorafenib tablets has not been established.

\*adverse reactions may have a life-threatening or fatal outcome.

†reported in 1.9% of patients treated with sorafenib tablets (N= 2276).

## 6.2 Postmarketing Experience

The following adverse reactions have been identified during postapproval use of sorafenib tablets. 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.

**Blood and lymphatic disorders:** Thrombotic microangiopathy (TMA)

**Dermatologic:** Stevens-Johnson syndrome and toxic epidermal necrolysis (TEN)

**Hypersensitivity:** Angioedema

**Musculoskeletal:** Rhabdomyolysis, osteonecrosis of the jaw

**Respiratory:** Interstitial lung disease-like events (which may have a life-threatening or fatal outcome)

**Vascular:** Arterial (including aortic) aneurysms, dissections, and rupture

## 7 DRUG INTERACTIONS

### 7.1 Effect of Other Drugs on Sorafenib Tablets

### Strong CYP3A4 Inducers

The concomitant use of sorafenib tablets with rifampin, a strong CYP3A4 inducer decreased the mean AUC of sorafenib, which may decrease the antitumor activity [see Clinical Pharmacology (12.3)]. Avoid concomitant use of sorafenib tablets with strong CYP3A4 inducers, when possible, because these drugs can decrease the systemic exposure to sorafenib.

### Neomycin

The concomitant use of sorafenib tablets with neomycin decreased the mean AUC of sorafenib, which may decrease the antitumor activity. Avoid concomitant use of sorafenib tablets with neomycin. The effects of other antibiotics on the pharmacokinetics of sorafenib have not been studied [see Clinical Pharmacology (12.3)].

## **7.2 Concomitant Use of Warfarin**

The concomitant use of sorafenib tablets and warfarin may increase the risk of bleeding or increased the INR. Monitor INR and for clinical bleeding episodes in patients taking warfarin while receiving sorafenib tablets [see Warnings and Precautions (5.6)].

## **7.3 Drugs That Prolong the QT Interval**

Sorafenib tablets are associated with QTc interval prolongation. Avoid coadministration of sorafenib tablets with medicinal products with a known potential to prolong QT/QTc interval [see Warnings and Precautions (5.9), Clinical Pharmacology (12.2)].

## **8 USE IN SPECIFIC POPULATIONS**

### **8.1 Pregnancy**

#### Risk Summary

Based on findings from animal studies and its mechanism of action [see Clinical Pharmacology (12.1)], sorafenib tablets may cause fetal harm when administered to a pregnant woman. There are no available data in pregnant women to inform a drug-associated risk. In animal reproduction studies, oral administration of sorafenib to pregnant rats and rabbits during the period of organogenesis resulted in embryo-fetal toxicities at maternal exposures that were significantly lower than human exposures at the recommended dose of 400 mg twice daily (see Data). Advise pregnant women and females of reproductive potential of the potential risk to a fetus.

The background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

#### Data

##### *Animal Data*

In animal reproduction studies, sorafenib was teratogenic and induced embryo-fetal toxicity (including increased post-implantation loss, resorptions, skeletal retardations, and retarded fetal weight) when administered orally to pregnant rats and rabbits during the period of organogenesis. The effects occurred at doses considerably below the recommended human dose of 400 mg twice daily (approximately 500 mg/m<sup>2</sup>/day on a body surface area basis). Adverse intrauterine development effects were seen at doses >0.2 mg/kg/day (1.2 mg/m<sup>2</sup>/day) in rats and ≥0.3 mg/kg/day (≥3.6 mg/m<sup>2</sup>/day) in rabbits. These doses result in exposures (AUC) that are approximately 0.008 times the AUC in patients at the recommended dose.

### **8.2 Lactation**

#### Risk Summary

There are no data on the presence of sorafenib or its metabolites in human milk, or its effects on the breast-fed child or on milk production. Sorafenib was present in milk of lactating rats (see Data). Because of the potential for serious adverse reactions in a breastfed child from sorafenib, advise women not to breastfeed during treatment with sorafenib and for 2 weeks after the last dose.

#### Data

##### Animal Data

Following administration of radiolabeled sorafenib to lactating Wistar rats, approximately 27% of the radioactivity was secreted into milk. The milk to plasma AUC ratio was approximately 5:1.

### **8.3 Females and Males of Reproductive Potential**

Sorafenib tablets may cause fetal harm when administered to a pregnant woman [see Use in Specific Populations (8.1)].

#### Pregnancy Testing

Verify the pregnancy status of females of reproductive potential prior to the initiation of sorafenib tablets.

#### Contraception

##### *Females*

Advise females of reproductive potential to use effective contraception during treatment and for 6 months following the last dose of sorafenib tablets.

##### *Males*

Based on genotoxicity and findings in animal reproduction studies, advise males with female partners of reproductive potential and pregnant partners to use effective contraception during treatment with sorafenib tablets and for 3 months following the last dose of sorafenib tablets [see Use in Specific Populations (8.1), Nonclinical Toxicology (13.1)].

#### Infertility

##### *Males*

Based on findings in animal studies, sorafenib tablets may impair fertility in males of reproductive potential [see *Nonclinical Toxicology (13.1)*].

### **8.4 Pediatric Use**

The safety and effectiveness of sorafenib tablets have not been established in pediatric patients.

#### Juvenile Animal Toxicity Data

Repeat dosing of sorafenib to young and growing dogs resulted in irregular thickening of the femoral growth plate at daily sorafenib doses  $\geq 600$  mg/m<sup>2</sup> (approximately 0.3 times the AUC at the recommended human dose), hypocellularity of the bone marrow adjoining the growth plate at 200 mg/m<sup>2</sup>/day (approximately 0.1 times the AUC at the recommended human dose), and alterations of the dentin composition at 600 mg/m<sup>2</sup>/day. Similar effects were not observed in adult dogs when dosed for 4 weeks or less.

### **8.5 Geriatric Use**

In total, 59% of HCC patients treated with sorafenib tablets were age 65 years or older and 19% were 75 and older. No differences in safety or efficacy were observed between older and younger patients, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater

sensitivity of some older individuals cannot be ruled out.

## 8.6 Renal Impairment

No dose adjustment is necessary for patients with mild, moderate or severe renal impairment who are not on dialysis. The pharmacokinetics of sorafenib have not been studied in patients who are on dialysis [see Clinical Pharmacology (12.3)].

## 8.7 Hepatic Impairment

No dose adjustment is necessary for patients with mild or moderate hepatic impairment. The pharmacokinetics of sorafenib have not been studied in patients with severe (Child-Pugh C) hepatic impairment [see Clinical Pharmacology (12.3)].

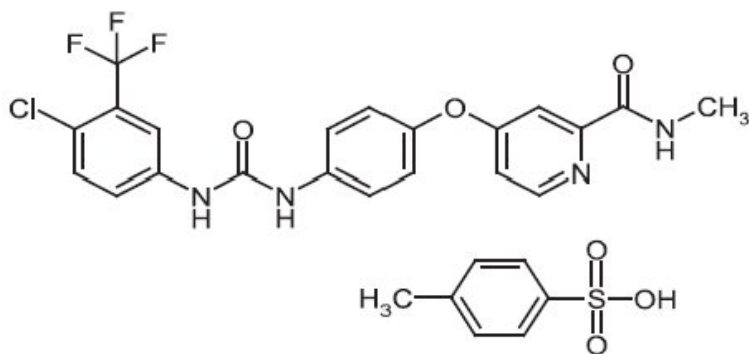
## 10 OVERDOSAGE

The adverse reactions observed at a dose of 800 mg twice daily (2 times the recommended dose) were primarily diarrhea and dermatologic. No information is available on symptoms of acute overdose in animals because of the saturation of absorption in oral acute toxicity studies conducted in animals.

In cases of suspected overdose, withhold sorafenib tablets and institute supportive care.

## 11 DESCRIPTION

Sorafenib, a kinase inhibitor, is the tosylate salt of sorafenib. Sorafenib tosylate has the chemical name 4-(4-{3-[4-Chloro-3-(trifluoromethyl)phenoxy]ureido}phenoxy)N2-methylpyridine-2-carboxamide 4 methylbenzenesulfonate. The molecular formula of sorafenib tosylate is  $C_{21}H_{16}ClF_3N_4O_3 \times C_7H_8O_3S$  and the molecular weight of sorafenib tosylate is 637.0 g/mole. Its structural formula is:



Sorafenib tosylate is a white to yellowish or brownish solid. Sorafenib tosylate is practically insoluble in aqueous media, slightly soluble in ethanol and soluble in PEG 400.

Sorafenib Tablets, USP for oral use is supplied as film-coated tablets containing 200 mg sorafenib equivalent to 274 mg sorafenib tosylate and the following inactive ingredients: croscarmellose sodium, ferric oxide red, hypromellose, magnesium stearate, microcrystalline cellulose, polyethylene glycol sodium lauryl sulphate, and titanium dioxide.

FDA approved dissolution test specifications differ from USP.

## 12 CLINICAL PHARMACOLOGY

### 12.1 Mechanism of Action

Sorafenib is a kinase inhibitor that decreases tumor 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, RET/PTC, VEGFR-1, VEGFR- 2, VEGFR- 3, and

PDGFR- $\beta$ ). Several of these kinases are thought to be involved in tumor cell signaling, angiogenesis and apoptosis. Sorafenib inhibited tumor growth of HCC and DTC human tumor xenografts in immunocompromised mice. Reductions in tumor angiogenesis were seen in models of HCC upon sorafenib treatment, and increases in tumor apoptosis were observed in models of HCC and DTC.

## 12.2 Pharmacodynamics

### Cardiac Electrophysiology

The effect of sorafenib tablets 400 mg twice daily on the QTc interval was evaluated in a multi-center, open-label, non-randomized trial in 53 patients with advanced cancer. No large changes in the mean QTc intervals (that is, >20 ms) from baseline were detected in the trial. After one 28-day treatment cycle, the largest mean QTc interval change of 8.5 ms (upper bound of two-sided 90% confidence interval, 13.3 ms) was observed at 6 hours post-dose on day 1 of cycle 2 [see *Warnings and Precautions (5.9), Drug Interactions (7.3)*].

## 12.3 Pharmacokinetics

Multiple doses of sorafenib tablets for 7 days resulted in a 2.5- to 7-fold accumulation compared to a single dose. Steady-state plasma sorafenib concentrations were achieved within 7 days, with a peak-to-trough ratio of mean concentrations of less than 2.

The steady-state concentrations of sorafenib following administration of sorafenib tablets 400 mg twice daily were evaluated in DTC and HCC patients. Patients with DTC have mean steady-state concentrations that are 1.8-fold higher than patients with HCC. The reason for increased sorafenib concentrations in DTC patients is unknown.

Mean  $C_{max}$  and AUC increased less than proportionally beyond oral doses of 400 mg administered twice daily.

### Absorption

After administration of sorafenib tablets, the mean relative bioavailability was 38–49% when compared to an oral solution. Following oral administration, sorafenib reached peak plasma levels in approximately 3 hours.

### *Effects of Food*

With a moderate-fat meal (30% fat; 700 calories), bioavailability was similar to that in the fasted state. With a high-fat meal (50% fat; 900 calories), bioavailability was reduced by 29% compared to that in the fasted state.

### Distribution

In vitro binding of sorafenib to human plasma proteins was 99.5%.

### Elimination

The mean elimination half-life of sorafenib was approximately 25 to 48 hours.

### *Metabolism*

Sorafenib undergoes oxidative metabolism by hepatic CYP3A4, as well as glucuronidation by UGT1A9.

### *Excretion*

Sorafenib accounted for approximately 70–85% of the circulating analytes in plasma at steady-state. Eight metabolites of sorafenib have been identified, of which 5 have been detected in plasma. The main circulating metabolite of sorafenib, the pyridine N-oxide that comprises approximately 9–16% of circulating analytes at steady-state, showed in vitro potency similar to that of sorafenib.

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 feces and 19% of the dose excreted in urine as glucuronidated metabolites. Unchanged sorafenib, accounting for 51% of the dose, was found in feces but not in urine.

### Specific Populations

A study of the pharmacokinetics of sorafenib indicated that the mean AUC of sorafenib in Asians (N=78) was 30% lower than in Whites (N=40). Sex and age do not have a clinically meaningful effect on the pharmacokinetics of sorafenib.



#### Patients with Renal Impairment

Mild (CLcr 50-80 mL/min), moderate (CLcr 30 - <50 mL/min), and severe (CLcr <30 mL/min) renal impairment do not affect the pharmacokinetics of sorafenib [see Use in Specific Populations (8.6)].

#### Patients with Hepatic Impairment

Mild (Child-Pugh A) and moderate (Child-Pugh B) hepatic impairment do not affect the pharmacokinetics of sorafenib [see Use in Specific Populations (8.7)].

#### Drug Interactions Studies

*Effect of Strong CYP3A4 Inhibitors on Sorafenib:* Ketoconazole, a strong inhibitor of CYP3A4 and P-glycoprotein, administered at a dose of 400 mg once daily for 7 days did not alter the mean AUC of a single oral dose of sorafenib tablet 50 mg in healthy subjects.

*Effect of Strong CYP3A4 Inducers on Sorafenib:* Concomitant use of sorafenib tablets with rifampin administered at a dose of 600 mg once daily for 5 days with a single oral dose of sorafenib tablets 400 mg in healthy volunteers resulted in a 37% decrease in the mean AUC of sorafenib.

*Effect of Neomycin on Sorafenib:* Neomycin administered as an oral dose of 1 g three times daily for 5 days decreased the mean AUC of sorafenib by 54% in healthy subjects administered a single oral dose of sorafenib tablets 400 mg.

*Effect of Sorafenib on Other Drugs:* sorafenib tablets 400 mg twice daily for 28 days did not increase the systemic exposure of concomitantly administered midazolam (CYP3A4 substrate), dextromethorphan (CYP2D6 substrate), and omeprazole (CYP2C19 substrate) [see Clinical Pharmacology (12.3)].

*Drugs that Increase Gastric pH:* The aqueous solubility of sorafenib is pH dependent, with higher pH resulting in lower solubility. However, omeprazole, a proton pump inhibitor, administered at a dose of 40 mg once daily for 5 days, did not result in a clinically meaningful change in sorafenib single dose exposure.

#### *In Vitro Studies*

Sorafenib competitively inhibited CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A4 in vitro. However, sorafenib tablets 400 mg twice daily for 28 days with substrates of CYP3A4, CYP2D6 and CYP2C19 did not increase the systemic exposure of these substrates [see Drug Interactions (7.3)].

Sorafenib did not increase CYP1A2 and CYP3A4 activities, suggesting that sorafenib is unlikely to induce CYP1A2 or CYP3A4 in humans.

Sorafenib inhibits glucuronidation by UGT1A1 and UGT1A9 in vitro. Sorafenib tablets could increase the systemic exposure of concomitantly administered drugs that are UGT1A1 or UGT1A9 substrates.

Sorafenib inhibited P-glycoprotein in vitro. Sorafenib tablets could increase the concentrations of concomitantly administered drugs that are P-glycoprotein substrates.

## **13 NONCLINICAL TOXICOLOGY**

### **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

Carcinogenicity studies have not been performed with sorafenib. Sorafenib was clastogenic when tested in an in vitro mammalian cell assay (Chinese hamster ovary) in the presence of metabolic activation. Sorafenib was not mutagenic in the in vitro Ames bacterial cell assay or clastogenic in an in vivo mouse micronucleus assay. One intermediate in the manufacturing process, which is also present in the final drug substance (<0.15%), was positive for mutagenesis in an in vitro bacterial cell assay (Ames test) when tested independently.

No specific studies with sorafenib have been conducted in animals to evaluate the effect on fertility. However, results from the repeat-dose toxicity studies suggest there is a potential for sorafenib to impair reproductive function and fertility. Multiple adverse effects were observed in male and female reproductive organs, with the rat being more

susceptible than mice or dogs. Typical changes in rats consisted of testicular atrophy or degeneration, degeneration of epididymis, prostate, and seminal vesicles, central necrosis of the corpora lutea and arrested follicular development. Sorafenib-related effects on the reproductive organs of rats were manifested at daily oral doses  $\geq 5$  mg/kg (30 mg/m<sup>2</sup>). This dose results in an exposure (AUC) that is approximately 0.5 times the AUC in patients at the recommended human dose. Dogs showed tubular degeneration in the testes at 30 mg/kg/day (600 mg/m<sup>2</sup>/day). This dose results in an exposure that is approximately 0.3 times the AUC at the recommended human dose. Oligospermia was observed in dogs at 60 mg/kg/day (1200 mg/m<sup>2</sup>/day) of sorafenib.

## 14 CLINICAL STUDIES

### 14.1 Hepatocellular Carcinoma

The SHARP (HCC) study (NCT00105443) was an international, multicenter, randomized, double blind, placebo-controlled trial in patients with unresectable hepatocellular carcinoma. Overall survival was the primary endpoint. A total of 602 patients were randomized; 299 to sorafenib tablets 400 mg twice daily and 303 to matching placebo. All 602 randomized subjects were included in the ITT population for the efficacy analyses.

Demographics and baseline disease characteristics were similar between the sorafenib tablets and placebo arms 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 tumor spread (30.1% vs. 30.0%), and Barcelona Clinic Liver Cancer stage (stage B: 18.1% vs. 16.8%; stage C: 81.6% vs. 83.2%; stage D: <1% vs. 0%). Liver impairment by Child-Pugh score was comparable between the sorafenib tablets and placebo arms (Class A: 95% vs. 98%; B: 5% vs. 2%). Only one patient with Child-Pugh class C was entered. Prior treatments included surgical resection procedures (19.1% vs. 20.5%), locoregional therapies (including radiofrequency ablation, percutaneous ethanol injection and transarterial chemoembolization; 38.8% vs. 40.6%), radiotherapy (4.3% vs. 5.0%) and systemic therapy (3.0% vs. 5.0%).

The trial was stopped for efficacy following a pre-specified second interim analysis for survival showing a statistically significant advantage for sorafenib tablets over placebo for overall survival (HR: 0.69, p= 0.00058) (see Table 10 and Figure 1). This advantage was consistent across all subsets analyzed.

Final analysis of time to tumor progression (TTP) based on data from an earlier time point (by independent radiologic review) also was significantly longer in the sorafenib tablets arm (HR: 0.58, p=0.000007) (see Table 10).

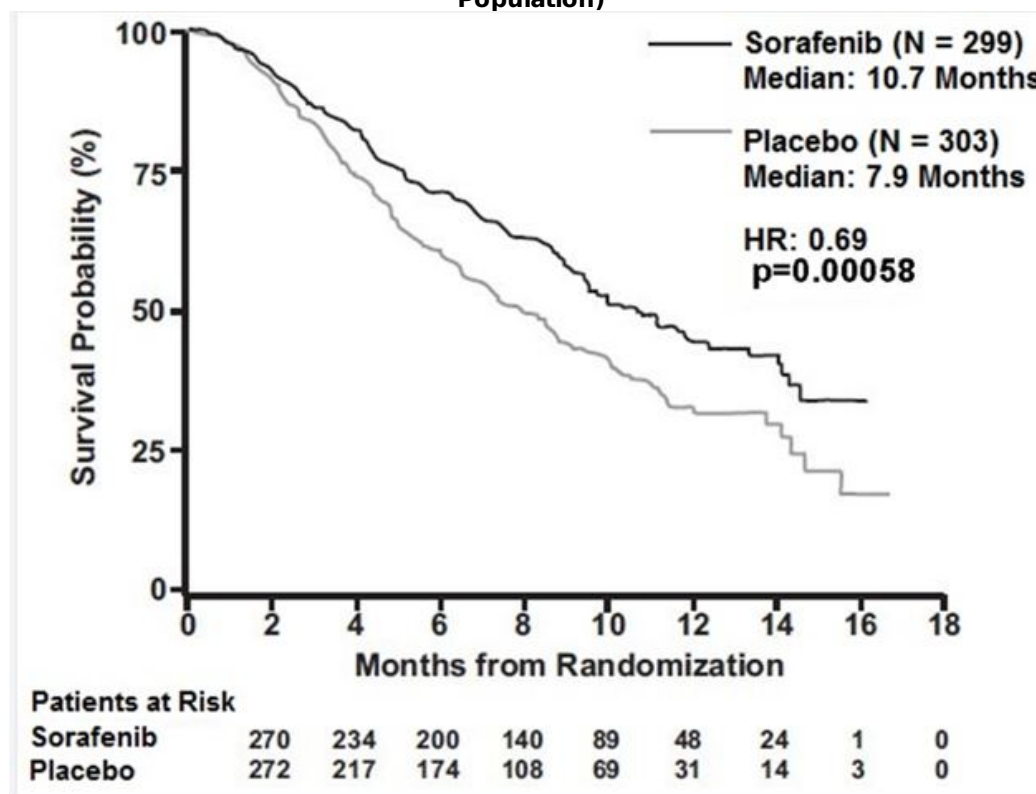
**Table 10: Efficacy Results from SHARP (HCC)**

<b>Efficacy Parameter</b>	<b>Sorafenib Tablets (N=299)</b>	<b>Placebo (N=303)</b>
<b>Overall Survival</b>		
Number of Events	143	178
Median, months	10.7	7.9
(95% CI)	(9.4, 13.3)	(6.8, 9.1)
Hazard Ratio <sup>1</sup> (95% CI)	0.69 (0.55, 0.87)	
P-value (log-rank test <sup>2</sup> )	0.00058	
<b>Time to Progression 3</b>		
Number of Events	107	156
Median, months	5.5	2.8
(95% CI)	(4.1, 6.9)	(2.7, 3.9)
Hazard Ratio <sup>1</sup> (95% CI)	0.58 (0.45, 0.74)	
P-value (log-rank test <sup>2</sup> )	0.000007	

CI=Confidence interval

1. Hazard ratio, sorafenib/placebo, stratified Cox model
2. Stratified log rank (for the interim analysis of survival, the stopping boundary one-sided  $\alpha = 0.0077$ )
3. The time-to-progression (TTP) analysis, based on independent radiologic review, was based on data from an earlier time point than the survival analysis

**Figure 1: Kaplan-Meier Curve of Overall Survival in SHARP (HCC) (Intent-to-Treat Population)**



### 14.3 Differentiated Thyroid Carcinoma

The safety and effectiveness of sorafenib tablets was evaluated in a multicenter, randomized (1:1), double-blind, placebo-controlled trial (DECISION; NCT00984282) conducted in 417 patients with locally recurrent or metastatic, progressive differentiated thyroid carcinoma (DTC) refractory to radioactive iodine (RAI) treatment. Randomization was stratified by age (< 60 years versus  $\geq 60$  years) and geographical region (North America, Europe, and Asia). All 417 subjects were included in the ITT population for the efficacy analyses.

All patients were required to have actively progressing disease defined as progression within 14 months of enrollment. RAI-refractory disease was defined based on four criteria that were not mutually exclusive. All RAI treatments and diagnostic scans were to be performed under conditions of a low iodine diet and adequate TSH stimulation. Following are the RAI-refractory criteria and the proportion of patients in the study that met each one: a target lesion with no iodine uptake on RAI scan (68%); tumors with iodine uptake and progression after RAI treatment within 16 months of enrollment (12%); tumors with iodine uptake and multiple RAI treatments with the last treatment greater than 16 months prior to enrollment, and disease progression after each of two RAI treatments administered within 16 months of each other (7%); cumulative RAI dose  $\geq 600$  mCi administered (34%). The major efficacy outcome measure was progression-free survival (PFS) as determined by a blinded, independent radiological review using a modified Response Evaluation Criteria in Solid Tumors v. 1.0 (RECIST). RECIST was modified by inclusion of clinical progression of bone lesions based on the need for external beam radiation (4.4% of progression events). Additional efficacy outcomes measures included overall survival (OS), tumor response rate, and duration of response.

Patients were randomized to receive sorafenib tablets 400 mg twice daily (n=207) or placebo (n=210). Of the 417 patients randomized, 48% were male, the median age was

63 years, 61% were 60 years or older, 60% were white, 62% had an ECOG performance status of 0, and 99% had undergone thyroidectomy. The histological diagnoses were papillary carcinoma in 57%, follicular carcinoma (including Hürthle cell) in 25%, and poorly differentiated carcinoma in 10%, and other in 8% of the study population. Metastases were present in 96% of the patients: lungs in 86%, lymph nodes in 51%, and bone in 27%. The median cumulative RAI activity administered prior to study entry was 400 mCi.

A statistically significant prolongation of PFS was demonstrated for sorafenib tablets - treated patients compared to those receiving placebo (Figure 3); no statistically significant difference was seen in the final overall survival (OS) analysis (Table 12). Crossover to open label sorafenib tablets occurred in 161 (77%) patients randomized to placebo after investigator-determined disease progression

**Table 12: Efficacy Results from DECISION in Differentiated Thyroid Carcinoma**

	<b>Sorafenib Tablets N = 207</b>	<b>Placebo N = 210</b>
<b>Progression-free Survival<sup>1</sup></b>		
Number of Deaths or Progression	113 (55%)	136 (65%)
Median PFS in Months (95% CI)	10.8 (9.1, 12.9)	5.8 ( 5.3, 7.8)
Hazard Ratio (95% CI)	0.59 (0.46, 0.76)	
P-value <sup>2</sup>	< 0.001	
<b>Overall Survival<sup>3</sup></b>		
Number of Deaths	103 (49.8%)	109 (51.9%)
Median OS in Months (95% CI)	42.8 (34.6, 52.6)	39.4 (32.7, 51.4)
Hazard Ratio (95% CI)	0.92 (0.71, 1.21)	
P-value <sup>2</sup>	0.570	
<b>Objective Response</b>		
Number of Objective Responders <sup>4</sup> (95% CI)	24 (12%) (7.6%, 16.8%)	1 (0.5%) (0.01%, 2.7%)
Median Duration of Response in Months (95% CI)	10.2 (7.4, 16.6)	NE

1 Independent radiological review

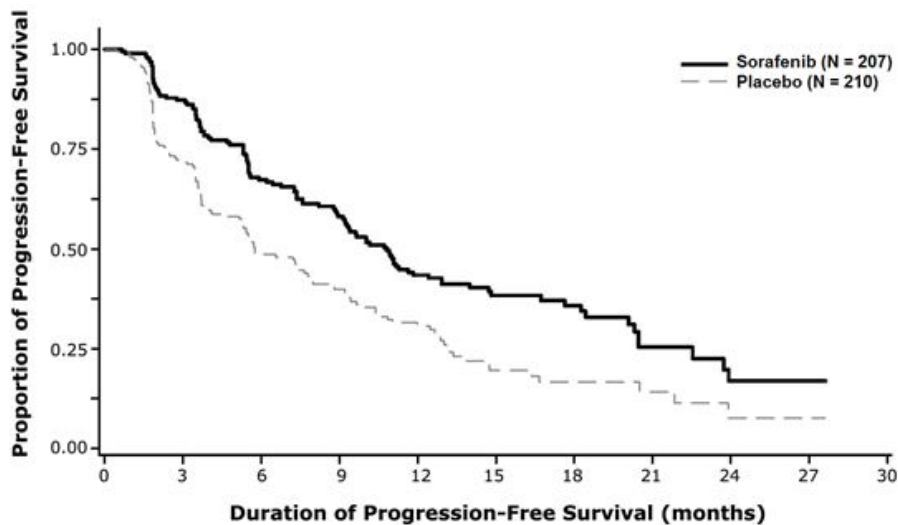
2 Two-sided log-rank test stratified by age (< 60 years, ≥ 60 years) and. geographic region (North America, Europe, Asia)

3 Conducted after 212 events, which occurred 36 months after the. primary PFS analysis.

4 All objective responses were partial responses

NR = Not Reached, CI = Confidence interval, NE = Not Estimable

**Figure 3: Kaplan-Meier Curve of Progression-Free Survival in DECISION (DTC)**



Patients at Risk

Sorafenib	207	159	115	91	60	35	27	13	5	2
Placebo	210	135	78	55	36	14	9	6	2	2

## 16 HOW SUPPLIED/STORAGE AND HANDLING

Sorafenib Tablets, USP are supplied as round, pink, film-coated tablets, debossed with “YB” on one side and “201” on the other side.

Bottles of 120 tablets NDC 24979-715-44

Bottles of 60 tablets NDC 24979-715-04

Store at 20°C to 25° C (68°F to 77° F); excursions permitted to 15°C to 30° C (59°F to 86° F) [see USP controlled room temperature]. Store in a dry place.

## 17 PATIENT COUNSELING INFORMATION

Advise the patient to read FDA-approved patient labeling (Patient Information).

### Cardiovascular Events

*Discuss with patients that cardiac ischemia and/or infarction and congestive heart failure, have been reported during sorafenib tablets treatment, and that they should immediately report any episodes of chest pain or other symptoms of cardiac ischemia or congestive heart failure [see Warnings and Precautions (5.1)].*

### Bleeding

*Inform patients that sorafenib tablets can increase the risk of bleeding and that they should promptly report any episodes of bleeding [see Warnings and Precautions (5.2)].*

*Inform patients that bleeding or elevations in the International Normalized Ratio (INR) have been reported in some patients taking warfarin while on sorafenib tablets and that their INR should be monitored regularly [see Warnings and Precautions (5.6)].*

### Hypertension

Inform patients that hypertension can develop during sorafenib tablets treatment, especially during the first six weeks of therapy, and that blood pressure should be monitored regularly during treatment [see Warnings and Precautions (5.3)].

### Skin Reactions

Advise patients of the possible occurrence of hand-foot skin reaction and rash during sorafenib tablets treatment and appropriate countermeasures [see Warnings and Precautions (5.4)].

### Gastrointestinal Perforation

Advise patients that cases of gastrointestinal perforation have been reported in patients taking sorafenib tablets [see Warnings and Precautions (5.5)].

#### Risk of Impaired Wound Healing

Advise patients that sorafenib tablets may impair wound healing. Advise patients to inform their healthcare provider of any planned surgical procedure [see Warnings and Precautions (5.7)].

#### QT Interval Prolongation

Inform patients with a history of prolonged QT interval that sorafenib tablets can worsen the condition [see Warnings and Precautions (5.9) and Clinical Pharmacology (12.2)].

#### Drug-Induced Liver Injury

Inform patients that sorafenib tablets can cause hepatitis which may result in hepatic failure and death. Advise patients that liver function tests should be monitored regularly during treatment and to report signs and symptoms of hepatitis [see Warnings and Precautions (5.10)].

#### Embryo-Fetal Toxicity

Advise females to inform their healthcare provider if they are pregnant or become pregnant. Inform female patients of the risk to a fetus and potential loss of pregnancy [see Use in Specific Populations (8.1)]. Advise females of reproductive potential to use effective contraception during treatment with sorafenib tablets and for 6 months after the last dose. Advise male patients with female partners of reproductive potential or who are pregnant to use effective contraception during treatment with sorafenib tablets and for 3 months after receiving the last dose of sorafenib tablets [see Warnings and Precautions (5.11), Use in Specific Populations (8.1, 8.3)].

#### Lactation

Advise patients not to breastfeed while taking sorafenib tablets and for 2 weeks after receiving the last dose of sorafenib tablets [see Use in Specific Populations (8.2)].

#### Missed Doses

Instruct patients that if a dose of sorafenib tablets is missed, the next dose should be taken at the regularly scheduled time, and not double the dose. Instruct patients to contact their healthcare provider immediately if they take too much sorafenib tablets.



Distributed by: TWi Pharmaceuticals USA, Inc.

Paramus, NJ 07652

Manufactured by: TWi Pharmaceuticals, Inc.

Taoyuan City, 320023, Taiwan

### **Patient Package Insert**

<p style="text-align: center;"><b>Patient Information</b> <b>Sorafenib (soe raf'e nib) Tablets, USP</b> <b>oral</b></p>
<p><b>What is sorafenib tablets?</b> Sorafenib tablets are a prescription medicine used to treat:</p> <ul style="list-style-type: none"><li>• a type of liver cancer called hepatocellular carcinoma (HCC) that cannot be removed by surgery</li><li>• a type of thyroid cancer called differentiated thyroid carcinoma (DTC) that can no longer be treated with radioactive iodine and is progressing</li></ul>

It is not known if sorafenib tablets are safe and effective in children.

**Do not take sorafenib tablets if you:**

- are allergic to sorafenib or any of the other ingredients in sorafenib tablets. See the end of this leaflet for a complete list of ingredients in sorafenib tablets.
- have squamous cell lung cancer and receive carboplatin and paclitaxel.

**Before taking sorafenib tablets, tell your healthcare provider about all of your medical conditions including if you:**

- have heart problems including a condition called “congenital long QT syndrome”
- have chest pain
- have abnormal magnesium, potassium, or calcium blood levels
- have bleeding problems
- have high blood pressure
- plan to have surgery or have had a recent surgery. You should stop taking sorafenib tablets at least 2 weeks before planned surgery. See “**What are the possible side effects of sorafenib tablets?**”
- are pregnant or plan to become pregnant. sorafenib tablets may harm your unborn baby. Tell your healthcare provider right away if you become pregnant during treatment with sorafenib tablets.

**For females** who are able to become pregnant:

o Your healthcare should do a pregnancy test before you start treatment with sorafenib tablets.

o Use effective birth control (contraception) during your treatment with sorafenib tablets and for 6 months after the last dose of sorafenib tablets.

**For males** with female partners who are able to become pregnant:

o Use effective birth control (contraception) during your treatment with sorafenib tablets and for 3 months after the last dose of sorafenib tablets.

• are breastfeeding or plan to breastfeed. It is not known if sorafenib tablets passes into your breast milk. Do not breastfeed during treatment with sorafenib tablets and for 2 weeks after receiving the last dose of sorafenib tablets

**Tell your healthcare provider about all the medicines you take**, including prescription and over-the-counter medicines, vitamins, and herbal supplements. Especially tell your healthcare provider if you take the medicine warfarin.

**How should I take sorafenib tablets?**

- Take sorafenib tablets exactly as your healthcare provider tells you to take it.
- Take sorafenib tablets 2 times a day. Your healthcare provider may change your dose, temporarily stop treatment or completely stop treatment with sorafenib tablets if you have side effects.
- Take sorafenib tablets without food (at least 1 hour before or 2 hours after a meal).
- If you miss a dose of sorafenib tablets, skip the missed dose, and take your next dose at your regular time. Do not double your dose of sorafenib tablets.
- If you take too much sorafenib tablets call your doctor or go to the nearest hospital emergency room right away.

**What are the possible side effects of sorafenib tablets?**

**Sorafenib tablets may cause serious side effects, including:**

- **decreased blood flow to the heart, heart attack and heart failure.** Get emergency help right away if you get symptoms such as chest pain, shortness of breath, racing heartbeat, swelling in lower legs, feet and abdomen, feel lightheaded or faint, tiredness, nausea, vomiting, or sweat a lot.
- **increased risk of bleeding. Bleeding is a common side effect of sorafenib tablets** that can be serious and can lead to death. Tell your healthcare provider right away if you have any signs of bleeding during treatment with sorafenib tablets:

- o vomiting blood or if your vomit looks like coffee-grounds
- o pink or brown urine or black (looks like tar) stools
- o coughing up blood or blood clots
- o heavier than normal menstrual cycle
- o unusual vaginal bleeding
- o frequent nose bleeds
- o bruising

- **high blood pressure. High blood pressure is a common side effect of**

**sorafenib tablets and can be serious.**Your blood pressure should be checked every week during the first 6 weeks of starting sorafenib tablets. Your blood pressure should be checked regularly and any high blood pressure should be treated during treatment with sorafenib tablets.

- **skin problems.** A condition called hand-foot skin reactions and skin rash are common with sorafenib tablets treatment and can be severe. Sorafenib tablets may also cause severe skin and mouth reactions that can be life-threatening. Tell your healthcare provider if you have any of the following symptoms:
  - o skin rash
  - o skin redness
  - o pain or swelling
  - o blistering and peeling of your skin
  - o blistering and peeling on the inside of your mouth
  - o blisters on the palms of your hand or soles of your feet
- **an opening in the wall of your stomach or intestines (gastrointestinal perforation).** Tell your healthcare provider right away if you get fever, nausea, vomiting or severe stomach (abdominal) pain.
- **risk of wound healing problems.** Wounds may not heal properly during sorafenib tablets treatment. Tell your healthcare provider if you plan to have any surgery before starting or during treatment with sorafenib tablets.
  - o You should stop taking sorafenib tablets at least 10 days before planned surgery.
  - o Your healthcare provider should tell you when you may start taking sorafenib tablets again after surgery.
- **changes in the electrical activity of your heart called QT prolongation.** QT prolongation can cause irregular heartbeats that can be life-threatening. Your healthcare provider may do tests during your treatment with sorafenib tablets to check the levels of potassium, magnesium, and calcium in your blood, and check the electrical activity of your heart with an electrocardiogram (ECG). Tell your healthcare provider right away if you feel faint, lightheaded, dizzy or feel your heart beating irregularly or fast during your treatment with sorafenib tablets.
- **liver problems (drug-induced hepatitis).** Sorafenib tablets may cause liver problems that may lead to liver failure and death. Your healthcare provider will do blood tests to check your liver function regularly during your treatment with sorafenib tablets. Tell your healthcare provider right away if you develop any of the following symptoms:

- o yellowing of your skin or the whites of your eyes
- o dark “tea-colored” urine
- o light-colored bowel movements (stools)
- o worsening nausea or vomiting
- o pain on the right side of your stomach
- o bleeding or bruising more easily than normal
- o loss of appetite

- **change in thyroid hormone levels.** If you have differentiated thyroid cancer, you can have changes in your thyroid hormone levels during treatment with sorafenib tablets. Your healthcare provider may need to change your dose of thyroid medicine during treatment with sorafenib tablets. Your healthcare provider should check your thyroid hormone levels every month during treatment with sorafenib tablets.

**The most common side effects of sorafenib tablets include:**

- o diarrhea (frequent or loose bowel movements)
- o tiredness
- o infection
- o hair thinning or patchy hair loss
- o rash
- o weight loss
- o loss of appetite
- o nausea
- o stomach-area(abdomen) pain
- o low blood calcium levels in people with differentiated thyroid cancer

Sorafenib tablets may cause fertility problems in males. This may affect your ability to father a child. Talk to your healthcare provider if this is a concern for you.

These are not all of the possible side effects of sorafenib tablets. Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

**How should I store sorafenib tablets?**

- Store at 20°C to 25° C (68°F to 77° F); excursions permitted to 15°C to 30° C (59°F



to 86° F) [see USP controlled room temperature].

- Store sorafenib tablets in a dry place.

**Keep sorafenib tablets and all medicines out of the reach of children.**

**General information about the safe and effective use of sorafenib tablets**

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use sorafenib tablets for a condition for which it is not prescribed. Do not give sorafenib tablets to other people even if they have the same symptoms you have. It may harm them. You can ask your healthcare provider or pharmacist for information about sorafenib tablets that is written for health professionals.

**What are the ingredients in sorafenib tablets?**

**Active Ingredient:** sorafenib tosylate

**Inactive Ingredients:** croscarmellose sodium, ferric oxide red, hypromellose, magnesium stearate, microcrystalline cellulose, sodium lauryl sulphate, polyethylene glycol, and titanium dioxide.



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Paramus, NJ 07652

Manufactured by: TWi Pharmaceuticals, Inc.

Taoyuan City, 320023, Taiwan

This Patient Information has been approved by the U.S. Food and Drug Administration.

Revised 05/2023

LA-3132-01

**Sorafenib tablets 200 mg Bottle Label**

**Rx Only**

**NDC 24979-715-44**

Sorafenib Tablets, USP

Each tablet contains

**200 mg**

sorafenib

120 Tablets



**SORAFENIB**

sorafenib tablet, film coated

Product Information				
<b>Product Type</b>	HUMAN PRESCRIPTION DRUG	<b>Item Code (Source)</b>	NDC:24979-715	
<b>Route of Administration</b>	ORAL			
Active Ingredient/Active Moiety				
Ingredient Name		Basis of Strength	Strength	
SORAFENIB (UNII: 9ZOQ3TZI87) (SORAFENIB - UNII:9ZOQ3TZI87)		SORAFENIB	200 mg	
Inactive Ingredients				
Ingredient Name			Strength	
CROSCARMELLOSE SODIUM (UNII: M28OL1HH48)				
MICROCRYSTALLINE CELLULOSE (UNII: OP1R32D61U)				
HYPROMELLOSE, UNSPECIFIED (UNII: 3NXW29V3WO)				
SODIUM LAURYL SULFATE (UNII: 368GB5141J)				
MAGNESIUM STEARATE (UNII: 70097M6I30)				
POLYETHYLENE GLYCOL, UNSPECIFIED (UNII: 3WJQ0SDW1A)				
TITANIUM DIOXIDE (UNII: 15FIX9V2JP)				
FERRIC OXIDE RED (UNII: 1K09F3G675)				
Product Characteristics				
<b>Color</b>	pink	<b>Score</b>	no score	
<b>Shape</b>	ROUND (ROUND)	<b>Size</b>	10mm	
<b>Flavor</b>		<b>Imprint Code</b>	YB;201	
<b>Contains</b>				
Packaging				
#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:24979-715-44	120 in 1 BOTTLE; Type 0: Not a Combination Product	12/01/2022	
Marketing Information				
Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date	
ANDA	ANDA209050	12/01/2022		

**Labeler** - TWi Pharmaceuticals, Inc. (658402052)

### Establishment

Name	Address	ID/FEI	Business Operations
Yabao Pharmaceutical Co., Ltd. Beijing		421252976	manufacture(24979-715)

### Establishment

Name	Address	ID/FEI	Business Operations
TWi Pharmaceuticals, Inc. Zhongli Plant		658863394	manufacture(24979-715)

Revised: 5/2023

TWi Pharmaceuticals, Inc.