文件名称	北生物-OEM-索拉非尼片USP, 200mg-通用说明书 2022.10.27 薛晶 P18803
成品尺寸	645mm×300mm 成品尺寸: 33mm×32mm
工艺要求	单色 双面胶印 K K发45度 175线以上
材质要求	40g胶版纸

HIGHLIGHTS OF PRESCRIBING INFORMATION THE ADDRESS OF TRESCRIBING 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

- 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)

--- DOSAGE FORMS AND STRENGTHS --

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

tablets. (2.2, 5.1)

<u>Hypertension</u>: Discontinue sorafenib tablets if needed. (5.2)

<u>Hypertension</u>: Monitor blood pressure weekly during the first 6 weeks and periodically thereafter. Consider temporary or permanent discontinuation for severe or persistent hypertension despite attily pertensive therapy. (5.3)

<u>Dermatologic Toxicities</u>: Interrupt and/or decrease dose. Discontinue for severe or

persistent reactions, or if Stevens-Johnson syndrome and toxic epidermal necrolysis is

persistent reactions, or if Stevens-Jonnson syndrome and toxic epidermal necrotysis is suspected. (5.1)

• Gastrointestinal Perforation: Discontinue sorafemib tablets, (5.5)

• Risk of Impaired Meand Healing: Withhold sorafemib tablets for at least 10 days prior to elective surgery. Do not administer for at least 2 weeks following major surgery and until electrointy surgery. The proposition of the state of the surgery of the surgery and the surgery and the surgery surgery. The surgery is the surgery of the surg

ADVERSE REACTIONS
The most common adverse reactions (>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 <a href="https://www.fda.gov/medswatch.">www.fda.gov/medswatch.</a>

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

USE IN SPECIFIC POPULATIONS -- Lactation: Advise women not to breastfeed. (8.2)

See 17 for PATIENT COUNSELING INFORMATION and FDA-Approved Patient Labeling.

Revised: 10/2022

### FULL PRESCRIBING INFORMATION: CONTENTS\*

- 1.3 Differentiated Thyroid Carcinoma
  2 DOSAGE AND ADMINISTRATION
- 2.2 Dosage Modifications for Adverse Re DOSAGE FORMS AND STRENGTHS
- CONTRAINDICATIONS
  WARNINGS AND PRECAUTIONS

- 5.3 Hypertension5.4 Dermatologic Tox
- Increased Risk of Bleeding with Concomitant Use of Warfarin
- 5.7 Risk of Impaired Wound Healing
   5.8 Increased Mortality Observed with Sorafenib Tablets Admini Combination with Carboplatin/Paclitaxel and Gemcitabine/Cisplatin in
- Squamous Cell Lung Cancer QT Interval Prolongation
- 5.10 Drug-Induced Liver Injury 5.11 Embryo-Fetal Toxicity
- 5.12 Impairment of Thyroid Stimulating Hormone Suppression in ed Thyroid Carcinoma
- 6 ADVERSE REACTIONS
- 6.1 Clinical Trials Experience 6.2 Postmarketing Experience

### FULL PRESCRIBING INFORMATION 1 INDICATIONS AND USAGE

### 1.1 Hepatocellular Carcinoma

Sorafenib tablets are indicated for the treatment of patients with unresectable henatocellular

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 2 DOSAGE AND ADMINISTRATION

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 Dosage Modifications for Adverse Reactions

Recommended Dosage Modifications
The recommended Dosage Modifications for adverse reactions are provided in Tables 1, 2, and 3.
Table1: Recommended Dosage Modifications for Adverse Reactions

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

- 7.3 Drugs That Prolong the QT Interval USE IN SPECIFIC POPULATIONS
- USE IN SPECIFIC POPULATIONS
  8.1 Pregnancy
  8.2 Lactation
  8.3 Females and Males of Reproductive Potential
  8.4 Pediatric Use
  8.5 Geriatric Use
  8.6 Renal Impairment

- 11 DESCRIPTION 12 CLINICAL PHARMACOLOGY
- 13 NONCLINICAL TOXICOLOGY
- s, Mutagenesis, Impairment of Fertility
- 14 CLINICAL STUDIES
  - OW SUPPLIED/STORAGE AND HANDLING
- 17 PATIENT COUNSELING INFORMATION

Sections or subsections omitted from the full prescribing information are not listed.

Table2: Recommended Dosage Modifications of Sorafenib Tablets for Adverse Reactions

[Adverse Reaction | Severity' | Sorafenib Tablets Dosage Modification

Adverse Reaction	Severny	Soratenio Tableis Dosage Modification
Cardiovascular Events [see War.	nings 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.
Hemorrhage [see Warnings and Precautions (5.2)]	Grade 2 and above requiring medical intervention	Permanently discontinue.
Hypertension [see Warnings and Procautions (3.3)]	Grade 2 (symptomatic/ persistent) OR Grade 2 symptomatic increase by greater than 20 mm Hg (diastolic) or greater than 14090 mm Hg if previously within normal limits OR Grade 3	Interrupt until symptoms 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>
	Grade 4	Permanently discontinue.
Gastrointestinal Perforation [see Warnings and Precautions (5.5)]	Any grade	Permanently discontinue.
QT Interval Prolongation [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.
Drug-Induced Liver Injury [see Warnings and Precautions (5.10)]	Grade 3 ALT or higher in the absence of another cause GOR AST/ALT greater than 3 × upper limit normal (ULN) with bilirubin greater than 2 × ULN in the absence of another cause GOR AST/ALT greater than 2 × ULN in the absence of another cause GOR AST/ALT greater than 2 × ULN in the absence of another cause GOR AST/ALT GRADE TO THE CAUSE GORD TO THE CAUSE	Permanently discontinue.

# Interrupt until Grade 2 or less, then at reduced dose by 1 dose level. Interrupt until Grade 2 or less, then re at reduced dose by 2 dose levels. OR 2<sup>rd</sup> or 3<sup>rd</sup> occurrence to occurrence

Adverse reactions graded according to National Cancer Institute Common Terminology Criteria for Adverse Events Version 3.0 VCE CTCAE-3.0 M.

If no recovery a the 50 day interruption, discontinue treatment unless the patient is deriving clinical benefit.

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

In addition, any grade increased alkaline phosphatase in the absence of known bone pathology and Grade 2 or worse increased billimbing, any 1 of the following: DNR of 1.5 or greater, ascites und/or encephalogathy in the absence of nuderlying cirrhosis or other organ failure considered to be also the dispersance of the following: DNR of 1.5 or greater, ascites and/or encephalogathy in the absence of underlying cirrhosis or other organ failure considered to be also to diago-inheced liver injusy.

B	Occurrence	Sorafenib Tablets I	Oosage Modification	
Dermatologic Toxicity Grade		Hepatocellular	Differentiated Thyroid Carcinoma	
Grade 2: Painful	1 <sup>st</sup> occurrence	Continue sorafenib tablets and consider topical therapy for symptomatic relief. If no improvement within 7 days, see below.	Decrease sorafenib tablets to 600 mg daily. If no improvement within 7 days, see below.	
erythema and swelling of the hands or feet and/ or discomfort affecting	No improvement within 7 days at	Interrupt sorafenib tablets until resolved or improved to Grade 0 to 1.	Interrupt sorafenib tablets until completely resolved or improve to Grade1.	
the patient's normal activities	reduced dose OR 2 <sup>nd</sup> and 3 <sup>nd</sup> occurrence	When resuming treatment, decrease dose by 1 dose level.	When resuming treatment, decrease dose by 1 dose level fo 2 <sup>rd</sup> occurrence and 2 dose levels for 3 <sup>rd</sup> occurrence.	
	4 <sup>ti</sup> occurrence	Discontinue sorafenib tablets treatment.		
Grade 3: Moist	1st occurrence	Interrupt sorafenib tablets until resolved or improved to Grade 0 to 1.	Interrupt sorafenib tablets until completely resolved or improve to Grade 1.	
desquamation, ulceration, blistering,		When resuming treatment, decrease dose by 1 dose level.	When resuming treatment, decrease dose by 1 dose level.	
or severe pain of the hands or feet, resulting in inability to work or nerform activities of	2 <sup>nd</sup> occurrence	Interrupt sorafenib tablets until resolved or improved to Grade 0 to 1.	Interrupt sorafenib tablets until completely resolved or improve to Grade 1.	
daily living		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 treat	fment	

Following improvement of Grade 2 or 3 dermatologic toxicity to Grade 0 for 1 for at least 28 days on a reduced dose of sortlemb tablets, the dose of sortlemb tablets may be increased 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 rolerate the higher dose the higher dose without recurrent Grade 2 or higher dematologic toxicity).

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

Sorafenib tablets are component of sorafenib tablets.

Sorafenib tablets are combination with carboplatin and paclitaxel are contraindicated in patients with sorafenib tablets in combination with carboplatin and paclitaxel are contraindicated in patients with squamous cell lung cancer [see Warnings and Precautions (5.8)].

WARNINGS AND PRECAUTIONS

Lacilitations for the contraint of the patients with squamous cell lung cancer [see Warnings and Precautions (5.8)].

### 5.1 Cardiovascular Events

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/finarction was 1.9% in the sorafenib tablets-treated group compared with 0% in patients receiving placebo. Patients with unstable coronary artery disease or recent unyocardial infarction was recluded 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 (6.21). N=2210] [see Adverse Reactions (0.2]].
onsider temporary or permanent discontinuation of sorafenib tablets in patients who develop ardiovascular events [see Dosage and Administration (2.2)].

5.2 Hemorrhage

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, sorafenib tablets in patients with DTC.

sorafemb tablets in patients with Execution of the State Patients of the State Patients and 4.3% of patients receiving placebo. In the DECISION (DTC) study, hypertension was reported in 40.6% of sorafemi bablets-treated patients and 1.24% 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 sorafemb tablets-treated patients in the SHARP (HCC) study, and 1 of 207 sorafemb 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 (2.3]].

Hand-foot skin reaction and rash represent the most common adverse reactions attribu sorafenib tablets. Rash and hand-foot skin reaction are usually Grade I and 2 and gen appear during the first six weeks of treatment with sorafenib tablets. Permanent discontin of therapy due to hand-hot skin reaction occurred in 4 felt-six of 207 sorafenib tablets patients with ICC, all I (6.3%) of 207 sorafenib ablets-treated patients with DTC.

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

5.6 Increased Risk of Bleeding with Concomitant Use of Warfarin

infrequent bleeding or elevations in the International Normalized Ratio (INR) have been rep a some patients taking warfarin while on sorafemib tablets. Monitor patients taking concor arfarin regularly for changes in prothrombin time (PT), INR or clinical bleeding episodes.

Impaired wound healing can occur in patients who receive drugs that inhibit the VEGF signaling pathway. Therefore, sorafenih tablets has the potential to adversely affect wound healing. Withhold sorafenih tablets for at least 10 days prior to elective surgery. Do not administer for at least 2 weeks following major surgery and mult adequate wound healing. The safety of resumption of sorafenih tablets after resolution of wound healing complications has not been established.

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

with Carboplatin/Paciltaxel and Gemeitabine/Usplatin in Squamous Cell Lung Cancer
In a subset analysis of two anomized controlled trials in chemo-naive patients with Stage
IIIB-IV non-small cell lung cancer, patients with squamous cell carcinoma experienced higher
mortality with he addition of soratenit bables compared to those treated with carboplatin/
paciltaxel alone (HR 1.81; 95% CI 1.19, 2.74) and genetiabine/cisplatin alone (HR 1.22;
95% CI 0.82, 1.80). The use of sorafenit bables in combination with carboplatin/paclitaxel is
contraindicated in patients with squamous cell lung cancer.

Sorafenib tablets in combination with gemcitabine/cisplatin is 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.

Seatons on particular with interest cell unique ancie.

5.9 QT Interval Prolongation

Sorafenib tablets can prolong the QT/QTe interval. QT/QTe interval prolongation increases the risk for ventricular arrhythmia.

risk for ventricular armythmus.

Avoid sorrafient blables in patients with congenital long QT syndrome. Monitor electrolytes and electrocardiograms in patients with congestive heart failure, bradyarrhythmiss, drugs known to prolong the QT interval, including Class Is and III antiarriphymiss. Cornect electrolyte about the properties of the properties of

5.10 Drug-Induced Liver Injury

5.10 Drug-Induced Liver Injury
Sornfeini-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 bilirabin and INR may also occur. The incidence of severe drug-induced liver injury, defined as elevated transamises levels shove 20 times the upper limit of hormal or transaminase elevations with significant clinical sequelee (for example, elevated INR, ascites, final, 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 sorafemb tablets [see Dosage and Administration (2.2)].
5.11 Embras-Rotal Tvaciety

5.11 Embryo-Fetal Toxicity

5.11 Embryo-Fetal Toxicity
Based on its mechanism of action and findings in animals, sorafemib tablets may cause fetal harm when administered to a pregnant woman. Sorafemib caused embryo-fetal toxicities in animals at maternal exposures at the recisiplificantly 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 fetas. Advise female so ferponductive potential to use effective contraception during treatment and for 6 months following the last dose of sorafemib tablets. Advises male contraception during treatment and for 6 months following the last dose of sorafemib tablets are effective contraception during treatment and for 3 months following the last dose of sorafemib tablets with the properties of the prop

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

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)]
- Typescusson (see trainings that it causins 12-2) in Demmalologic toxicities [see Warnings and Precountins (5.4)]
  Gastrointestinal perforation [see Warnings and Precountins (5.5)]
  OT interval prolongation [see Warnings and Precountins (5.9) and Clinical Pharmacology (12.2)]
  Drug-induced liver injury [see Warnings and Precountins (5.10)]

### irment of TSH suppression in DTC [see Warnings and Precautions (5.12)] 6.1 Clinical Trials Experience

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 sorafemib 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 (20%), which were considered to be related to sorafemib tablets, in patients with MCC or DTC are diarrhea, fatigue, infection, and abdominal pains, hypertension, and hemorrhage.
Hentoccollular Carcinoma

### 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 tablest-treated group than in those receiving placebo.

Adverse Reaction	N=297			N=302		
Adverse Reaction	All Grades %	Grade 3 %	Grade 4 %	All Grades	Grade 3 %	Grad
Any Adverse Reaction	98	39	6	96	24	- 8
Gastrointestinal						
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
Constitutional symptoms						
Fatigue	46	9	1	45	12	2
Weight loss	30	2	0	10	1	0
Pain						
Pain, abdomen	31	9	0	26	5	- 1
Dermatology/skin						
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
Hepatobiliary/pancreas						
Liver dysfunction	11	2	1	8	2	1

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)

Sorafenib Tablets

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. nd 1% of those receiving placebo. Hemorrhage/bleeding was reported in 18% of those receiving sorafenib tablets and 20% of tatients receiving placebo. The rates of Grade 3 and 4 bleeding were also higher in patients seceiving placebo (Grade 3 – 3% sorafenib tablets and 5% placebo and Grade 4 – 2% sorafenib ablets and 4% placebo.) Bleeding from esophageal varices was reported in 2.4% in sorafenib ablets-treated patients and 4% of patients receiving placebo.

Renal failure was reported in <1% of patients receiving placebo.

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

(Citauc 2).

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

Laboratory Parameter <sup>1</sup>		ib Tablets 297		cebo -302
Laboratory Parameter	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	35	11	11	2
Elevated Amylase	34	2	29	2
Hypocalcemia	27	2.4	15	1
Hypokalemia	10	<1	6	<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

Intercentained Introd Laremona

The safety of sonafenite bables 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 ablets (m-207) or matching placebo (m-209) until disease progression or intolerable toxicity in a double-blind trial face Chineal Stantes (H-1)/. The data described below reflect a median exposure to surdenib tablets had a median age of 63 years). The population exposed to sorafenib tablets was 50% nate, and base intermediations for adverse reasoning transfer and the surface of the s

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 teatment discontinuation were reported in 14% of patients. Adverse reactions that resulted in 1.4% of patients receiving placebo.

Table 8 shows the percentage of DTC patients experiencing adverse reactions at a higher rate in sorafemib tablets-treated patients than in patients receiving placebo in the double-bind phase of the DECISION study. Grade 3 adverse reactions occurred in 52% of sorafemib tables-treated patients compared to 25% of patients receiving placebo. Grade 4 adverse reactions occurred in 12% of sorafemib tables-treated patients or 10 % of patients receiving placebo.

Table 8: Selected Adverse Reactions Occurring at a Higher Incidence in Sorafenib Tablets-

ted Patients ween Arm Difference of  $\geq 5\%$  (All Grades)<sup>1</sup> or  $\geq 2\%$  (Grades 3 and 4)]

Adverse Reaction		= 207		: 209
Adverse Reaction	All Grades (%)	Grades 3 and 4 (%)	All Grades (%)	Grades 3 and 4 (%)
Skin and subcutaneous tiss	sue disorders			
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
Gastrointestinal disorders				
Diarrhea	68	6	15	1
Stomatitis <sup>3</sup>	24	2	3	0
Nausca	21	0	12	0

Abdominal pain <sup>2</sup>	20	1	7	1
Constipation	16	0	8	0.5
Oral pain <sup>d</sup>	14	0.5	6	0
Vomiting	11	0	3	0
Investigations				
Weight loss	49	6	14	1
General disorders and administra	tion site condition	s		
Fatigue	41	5	20	1
Asthenia	12	0	7	0
Pyrexia	11	1	5	0
Vascular disorders				
Hypertension <sup>6</sup>	41	10	12	2
Metabolism and nutrition disorde	rs			
Decreased appetite	30	2	5	0
Nervous system disorders				
Headache	17	0	6	0
Dysgeusia	6	0	0	0
Musculoskeletal and connective ti	ssue disorders			
Pain in extremity	15	1	7	0
Muscle spasms	10	0	3	0
Respiratory, thoracic and medias	tinal disorders			
Dysphonia	13	0.5	3	0
Epistaxis	7	0	1	0

Epistaxis

Neoplasmo benijan, malignant and unspecified

Squamous cell carcinoma of skin 3 0 0 0

National Cancer Institute Common Terminology Criteria for Adverse Events Version 3.0

Includes the following terms: abdominal pain, abdominal discomfort, hepatic pain, esophageal discomfort, abdominal pain lower, abdominal pain upper, abdominal tenderness, abdominal pain tower, abdominal pain upper, abdominal tenderness, abdominal pain tower.

Includes the following terms: oral pain, oropharyngeal discomfort, glossitis, burning mouth

yndrome, glossodynta
Palmar-plantar crythrodysesthesia syndrome (Hand-foot skin reaction)
Includes the following terms: hypertension, blood pressure increased, blood pressure systolic nereased increased

The relative increase for the following laboratory abnormalities observed in configuring tablesteated patients as compared to patients receiving placebo in the DECISION study is similar to
lymphopenia, anemia, and thromboeytopenia. Hypocalectmia was more frequent and more
severe in patients with DTC, especially those with a history of hypographyroidism, compared to
patients with HCC. Other laboratory test abnormalities reported in DECISION are presented in
Table 9.

		b Tablets 207		cebo 209
Laboratory Parameter <sup>1</sup>	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

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 10% and 10% or greater.

Cardiovascular: Common: congestive heart failure\*†, 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, gastrioit, gastrioitestinal perforations\*, cholecystitis, chalangitis 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 illineral.

natologic: Very common: leukopenia, lymphopenia Common: anemia, neu mbocytopenia Uncommon: INR abnormal Hepatobiliary disorders: Rare: drug-induced liver injury (including hepatic failure and death)

ypersensitivity: Uncommon: hypersensitivity reactions (including skin reactions and urticaria), applylactic reaction Metabolic and Nutritional: Very common: hypophosphatemia Common: transient increases in transaminases, hypocaleemia, hypokalemia, hypotalemia, hypothyroidism Uncommon: dehydration, transient increases in alkaline phosphatase, increased bilirubin (including jaundice),

Musculoskeletal: Very common: arthralgia Common: myalgia, muscle spasn

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) patinomiss and using inframination).

In addition, the following medically significant adverse reactions were uncommon clinical trials of sorafenib tables: transient ischemic attack, arrhythmia, and thromboem For these adverse reactions, the causal relationship to sorafenib tablets has not been establ \*adverse reactions may have a life-threatening or fatal outcome.

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

As 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)

Musculoskeletal: Rhabdomyolysis, osteonecrosis of the jaw

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

uding aortic) aneurysms, dissections, and rupture

### 7 DRUG INTERACTIONS

### 7.1 Effect of Other Drugs on Sorafenib Tablets ong CYP3A4 Inducers

Strong CYF3A4 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 nossible, because these drugs can decrease the systemic exposure to sorafenib.

7.2 Concommant 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 tablest *[sew Warmings and Precandings (3.6)]*.

### 7.3 Drugs That Prolong the QT Interval

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

### Risk Summary

Risk Summary

Based on findings from animal studies and its mechanism of action/see Clinical Pharmacology
(12.11), sorafemb 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 sorafemis 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
regnant 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 in
the stimated background risk of major brith defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Data

### Animal Data

Animal Data II an 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 roganogenesis. The effects occurred at doses considerably below the recommended human dose of 400 mg twice daily (approximately 500 mg/m²/day on aboby surface area, abasis). Adverse instruterine development effects were seen at doses-62, 2mg/kg/day (1.2 mg/m²/day) in rats and ≥0.3 mg/kg/day (1.2 mg/m²/day) in rabbits. These doses result in exposures (AUC) that are approximately 0.008 times the AUC in patients at the recommended dose.

### Risk Summary

 $\oplus$ 

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.

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

of the radioactivity was secreted into milk. The milk to plasma AUC ratio was approximately 3:1.

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)].

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

### Contraception

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

Dates 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 sorafenit hablets and for 3 months following the last dose of sorafenit bablets free Use in Specific Populations (8.1), Nonclinical Toxicology (13.1)].

### Infertility

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

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

### Juvenile Animal Toxicity Data

<u>Authentic Annual Toxicity Data</u>

Repeat dosing of sorafenib to young and growing dogs resulted in irregular thickening of the femoral growth plate at adaly sorafenib doses ≥600 mg/m² (approximately 0.3 times the AUC at the recommended human dose), hopecullularity of the bone marrow adjoining the growth plate at 200 mg/m²/day (approximately 0.1 times the AUC at the recommended human dose), and alterations of the deniar composition at 900 mg/m²/day. Similar effects were not observed in adult dogs when dosed for 4 weeks or less.

adult dogs when dosed for 4 weeks or reco.

8.5. Geriafric Use

In total, 59% of HCC patients treated with sorafenit tablets were age 65 years or older and 19% were 75 and older. No differences insafety or efficacy were observed between older and younger has not been sufficed differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be a control of the patients.

No dose adjustment is necessary for patients with mild, moderate or severe renal impairm who are not on dialysis. The pharmacokinetics of sorafenib have not been studied in patie 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 fsee Clinical Pharmacology (12.3). 10 OVERDOSAGE

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

Sorafenib, a kinase inhibitor, is the tosylate salt of sorafenib. Sorafenib tosylate has the chemical name 4-(4-13-[4-Chloro-3-t (trifluoromethyl ]phenyl[ureido]phenoxy]N2-methylpyriding-2-carboxamide 4-methylbenzensulfonate. The molecular formula of sorafenib tosylate is C<sub>3</sub>H<sub>∞</sub>(F<sub>1</sub>N<sub>O</sub>, x C<sub>3</sub>H<sub>o</sub>O<sub>5</sub> 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 Tables, 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: croscamellose sodium, ferric oxide red, hypomellose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, sodium lauryl sulphate, and titanium dioxide.

### FDA approved dissolution test specifications differ from USP. 12 CLINICAL PHARMACOLOGY

12 CLISMCA. PHANACOLOGY
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-CRAE, BRAF and mutant BRAF) and cell surface kinases (KIT, FLT-3, RET, RET/PTC, VEGFR-1, VEGFR-2, VEGFR-3, and PDGFR-8). Several of these kinases are thought to be involved in numor 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

### Cardiac Electrophysiology

<u>National Friedrichmystology</u>. The effect of sonafeibit tablets 400 mg twice daily on the QTc interval was evaluated in a multi-center, open-label, non-randomized trial in 33 patients with advanced cancer. No large changes in the mean QTc intervals (that is, 250 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 Warmings and Precoations (7.9), Drug Interactions (7.3)].

### 12.3 Pharmacokinetics

12.3 Pharmacokinetics

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

The steady-state concentrations of sorafreinb following administration of sorafreinb tablets may be a found to the concentrations of the properties. Patients with DTC have mean steady-state concentrations that are 1.8-fold higher than patients with HCC. The reason for increased sorafreinb concentrations in DTC patients is unknown.

Mean C<sub>max</sub> and AUC increased less than proportionally beyond oral doses of 400 mg administred twice daily.

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.

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

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

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-xotic that comprises approximately 9-16% of circulating analytes at steady-state, showed in vitro potency similar to that of sorafenib.

that of soratento.

Following oral administration of a 100 mg dose of a solution formulation of sorafen the dose was recovered within 14 days, with 77% of the dose excreted in feces and dose excreted in urine as glucuronidated metabolites. Unchanged sorafenib, accounting 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

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

pharmacokinetics of sorafemb fsee Use in Specific Populations (8.7)].

<u>Pure Interactions Studies</u>

<u>Effect of Strong CYP3.44 Inhibitors on Sorafenib</u>: Ketoconazole, a strong inhibitor of CYP3.44

and Pglycoprotein, 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 batles 50 mg in healthy subjects orafenib tables with

rifampin administered at a dose of 600 mg once daily for 5 days with a single oral dose of

sorafenib tables 400 mg in healthy volunteers resulted in a 37% decrease in the mean AUC of

sorafenib tables.

Effect of Sortgains on Other Druges. Sorafenib tablets 400 mg twice daily for 28 days did not increase the systemic exposure of concomitantly administered midazolam (CYP3A4 substrate), demonstrated midazolam (CYP3A4 substrate), and omeprazole (CYP2C19 substrate) free Clinical Fluormacology (12.3).

Institution of the American Conference of the Am

in vitro sinuaes. Soxiafenib 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

Sorafenib did not increase CYP1A2 and CYP3A4 activities, suggesting that sorafenib is unlikely to induce CYP1A2 or CYP3A4 in humans. Sorafenib inhibits glucuronidation by UGTIA1 and UGTIA9 in vitro. Sorafenib tablets could increase the systemic exposure of concomitantly administered drugs that are UGTIA1 or UGTIA9 substrates.

COLIA/S susualates.

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

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
Carcinogeneity studies have not been performed with conferals. Sorafenib was classogenic when tested in an in vitro mammalian cell assay (Chinese hauster ovary) in the presence of metabolic activation. Sorafenib was not mutageneit in the in vitro Ames bacterial cell assay or classogenic in an in vitro Ames bacterial cell assay or classogenic in an in vitro Ames bacterial cell assay or classogenic in a in vitro bacterial cell assay (Ames test) when tested independently.

No specific studies with sorafenib have been conducted interminate to evaluate the effect on so specific studies with sorafenib have been conducted interminate to evaluate the effect on sorafenib to impair reproductive function and fertility, Multiple adverse effects were observed in male and fernale reproductive function and fertility, Multiple adverse effects were observed in male and fernale reproductive organs, with the rat being more susceptible than mice or dogs. Typical changes in rats consisted of testicular atrophy or degeneration, degeneration, degeneration of priddymis, prostate, and seminal vesselse, central necrosis of the corpora latera and arrested follicular development. Sorafenib-related effects on the reproductive organs of rats were follicular development and the composition of th

### 14.1 Hepatocellular Carcinoma

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 tables 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 between the anal aclotobic liver disease), ITMS taking (stage): e1749 vs. x. 1748, stage in: 10.478 vs. x. 355, stage iii: 37.878 vs. x. 4568, stage (stage): e1749 vs. x. 1748, stage iii: 10.478 vs. x. 355, stage iii: 37.878 vs. x. 4568, stage (stage): e1749 vs. x. 1748, stage iii: 10.478 vs. x. 355, stage iii: 10.478 vs. x. 3568, stage; 11.5788 vs. x. 4568, stage (stage): x. 4578 vs. x. 4788, stage iii: 10.478 vs. x. 3578 vs. x. 4568, stage iii: 10.478 vs. x. 4578 vs. x. 4588 v

vs. 5.0%).

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

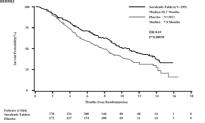
Final analysis of time to tumor progression (TTP) based on data from an earlier time point (by independent radiologic review) also was significantly longer in the sorafenib tablets arm (HR: 0.58, p=0.00007) (see Table 10).

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

Efficacy Parameter	Sorafenib Tablets (N=299)	Placebo (N=303)
Overall Survival		
Number of Events	143	178
Median, months	10.7	7.9
(95% CI)	(9.4, 13.3)	(6.8, 9.1)
Hazard Ratio (95% CI)	0.69 (0.55, 0.87)	
P-value (log-rank test <sup>2</sup> )	0.00058	
Time to Progression <sup>3</sup>		
Number of Events	107	156
Median, months	5.5	2.8
(95% CT)	(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> )	0.0000	107

Hazard ratio, sorafenib placebo, stratified Cox model
Stratified log rank (for the interim analysis of survival, the stopping boundary one-sided alpha 0.0077)

time-to-progression (TTP) analysis, based on independent radiologic review, was based on from an earlier time point than the survival analysis



(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 ≥ 60 years) and geographical region (North America, Europe, and Asia). All 417 subjects were included in the 117 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 imtually exclusive. All RAI treatments and diagnostic seams were to be performed under conditions of a low iodine diet and adequate TSI4 stimulation. Following are the RAI-refractory disease was defined based on four criteria that were not imtually exclusive. All RAI treatments and diagnostic seams were to be performed under conditions of a low iodine diet and adequate TSI4 stimulation. Following are the RAI-refractory disease was defined based on four criteria that the conditions of the progression and the production of the progression and the production of the results of the res

A statistically significant prolongation of PFS was demonstrated for sorafenib tables-tree patients compared to those receiving placebo (Figure 3); no statistically significant prolonger was seen in the final overall survival (QS) analysis; Gable 12). Crossover to open label sorafe tablets occurred in 161 (77%) patients randomized to placebo after investigator-determinidesaes progression.

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

	Sorafenib Tablets N=207	Placebo N=210	
Progression-free Survival <sup>1</sup>			
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 (0.4	46, 0.76)	
P-value <sup>2</sup>	<0.	001	
Overall Survival <sup>3</sup>			
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 (0.7	71, 1.21)	
P-value <sup>2</sup>	0.570		
Objective Response			
Number of Objective Responders <sup>4</sup>	24 (12%)	1 (0.5%)	
(95% CI)	(7.6%, 16.8%)	(0.01%, 2.7%)	
Median Duration of Response in Months (95% CI)	10.2 (7.4, 16.6)	NE	

mucpennum radiological review fwo-sided log-rank test stratified by age (< 60 years,  $\ge$  60 years) and geographic region (North ica,Europe, Asia)
aducted after 212 events, which occurred 36 months after the primary PFS analysis, objective responses were partial responses.
Not Reached, CI = Confidence interval, NE = Not Estimable

### on-Free Survival in DECISION (DTC)



16 HOW SUPPLIED/STORAGE AND HANDLING Sorafenib Tablets, USP are supplied as round, pink, film-coated tablets, debossed with "YB" one side and "201" on the other side.

Bottles of 120 tablets NDC 24979-715-44

Bottles of 60 tablets NDC 24979-715-04

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

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

Hypertension

### Advise the patient to read FDA-approved patient labeling (Patient Infor

Advise the patient to read PDA-approves parameters. Cardiovascular Events
Discuss with patients that cardiac ischemia and/or infarction and congestive heart failure, have been reported during soratemic hables teatment, and that they should immediately report any been reported during soratemic bales to the properties of cardiac ischemia or congestive heart failure face Warnings and Precautions (5.11).

Bleesting.

Inform patients that sorafenib tablets can increase the risk of bleeding and that they should promptly report any episodes of bleeding fisee Warnings and Precountons (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 Precountors (5.6).

# INFORMATION THE PROPERTY OF TH

ouring treatment yee warrangs and r recutations (3.3)].

Skin Reactions
Advise patients of the possible occurrence of hand-foot skin reaction and rash during sorafent tablets treatment and appropriate countermeasures [see Warrangs and Precautions (3.4)].

Gastrointestinal Perforation

Advise patients that cases of gastrointestinal perforation have been reported in pat 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 ealthcare provider of any planned surgical procedure [see Warnings and Precautions (5.7)]. OT Interval Prolongation

condition [see Warnings and Precautions (3:9) and Clinical Pharmacology (12.2)].

Pung-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 (3:10)].

Embroo-Feal Toxicity

Advise Emptach in Form their healthcare provides (if they are proposed to become proposed).

Embryo-Fedal Loxicity
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 sorafemit bablets 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 sorafemit bablets and for 3 months after receiving the last dose of sorafemit bablets (see Warnings and Precundous (s.1)). Use in Specific Populations (8.1, 8.3):

the last core or Sociation — 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 to much sorafenib tablets.

# Manufactured by: Yabao Pharmaceutical Co., Ltd. Beijing Beijing, China 101111

Distributed by: TWi Pharmaceuticals USA, Inc. Paramus, NJ 07652

### Patient Package Insert

# Patient Information Sorafenib (see raf' e nib) Tablets, USP oral

### What is sorafenib tablets?

max is soratenib tablets?

orafenib tablets are a prescription medicine used to treat:
a type of liver cancer called hepatocellular carcinoma (HCC) that cannot be removed be surrory. surgery
a type of thyroid cancer called differentiated thyroid carcinoma (DTC) that can no longer
treated with radioactive iodine and is progressing
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 the 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 medica

- and the same solution tables, tell you meanited to provide about an of 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

- nave bleeding problems have high blood pressure plant have high blood pressure plant have suggery 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?" AURICES.

  The pregnant or plan to become pregnant. Sorafenib tablets may harm your unborn baby. Tell our healthcare provider right away if you become pregnant during treatment with sorafenib
- iablets.

  To females who are able to become pregnant:

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

  Your healthcare should do a pregnancy test before you start treatment with sorafenib tablets and for 6 months after the last dose of sorafenib tablets.

  or males with fermale partners who are able to become pregnant:

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

  To 3 months after the last dose of sorafenib tablets and for 3 months after the last dose of sorafenib tablets and for 3 months after the last dose and adming treatment with sorafenib tablets and for 2 weeks after the start of the sorafenib tablets and for 2 weeks after the start of the sorafenib tablets and for 2 weeks after the start of the start of the sorafenib tablets and for 2 weeks after the start of the start of the sorafenib tablets and for 2 weeks after the start of the star
- breast fills. Do not treastract dourn guerantem want structure authorized and to a receiving the last dose of sorafemb tablets.

  Tell your healthcare provider about all the medicines you take, including prescription an 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 dost temporarily stop treatment or completely stop treatment with sorafenib tablets if you have si
- fficets.

  Aike sorafemib tablets without food (at least 1 hour before or 2 hours after a meal).

  Fyou miss a dose of sorafemib tablets, skip the missed dose, and take your next dose at you gualar time. Do not double your dose of sorafemib tablets.

  Fyou take too much sorafemib tablets call your doctor or go to the nearest hospital emergeneous right away.

- What are the possible side effects of sorafenib tablets?

  Sorafenib tablets may cause serious side effects, including:

  decreused 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, triedness, nausea, voniting, or sweat is
- lot.

  micreased 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 heavier than normal menstrual cycle ounsual vaginal bleeding pink or brown urine requested to the pink or brown urine requested to black (looks like tar) stools bruising

  o coughing up blood or blood dotlos

- o coughing up blood or blood clots high blood pressure. High blood pressure is a common side effect of sorafenib tablets an can be serious. Your blood pressure should be checked every week during the first 6 weeks o starting sorafenib tablets. Your blood pressure should be hecked regularly and any high bloo pressure should be treated during treatment with sorafenib tablets. skin problems. A condition called hand-foot skin reactions and skin rash are common wit sorafenib tablets treatment and can be severe. Sorafenib tablets may also cause severe skin an
- rafenib tablets treatment and can be severe. Sorafenib tablets may also cause severe south reactions that can be life-threatening. Tell your healthcare provider if you have

- skin rash
  skin redness
  pain or swelling
  pistering and peeling of your skin
  blistering and peeling on the inside of your mouth
  blistering and peeling on the inside of your mouth
  blistering and peeling on the inside of your feet
  an opening in the wall of your stomach or intestines (gastrointestinal perforation). To
  your healthcare provider right away if you get fever, nausea, vomiting or severe stoma
- (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 sorafenibe bablets.

  o You should stop taking sorafenib tablets at least 10 days before planned surgery.

  o You 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 heartheast that can be life-threatening. Your healthcare provider may do tests during your treatment with sorafeinh tablest to check the levels of potassium, magnesium, and calcium in your blood, and check the electrical activity of your heart with an electrocardingram (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
- sorafemb tables.

  Were problems (drug-induced hepatitis). Sorafemb 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 sorafemb tablets. Tell your healthcare provider right away if you develop any of the following symptoms:
- yellowing of your skin or the whites of your
  yellowing of your skin or the whites of your
  yellowing of your skin or the whites of your
  obleding or bruising more easily than no
  loss of appetite
- ments (stools) O worsening nausea or vomiting - 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:

- diarrhea (frequent or loose bowel weight loss
   loss of appetite

o tiredness
o infection
o infection
o hair thinning or patchy hair loss
o rash
o rash
Sorafemb 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 sorafemb 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) [se 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 sorafenit bablets 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.

Active Ingredient: sorafenib tosylate
Inactive Ingredients: croscarmellose sodium, ferric oxide red, hypromellose, magnes
stearate, mierocrystalline cellulose, sodium lauryl sulphate, polyethylene glycol, and titan

Manufactured by: Yabao Pharmaceutical Co., Ltd. Beijing Beijing, China 191111 Distributed by: TWI Pharmaceuticals USA, Inc. Paramus, NJ 07652

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

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