60-75 GSM MAPLITHO PAPER

171 mm x 255 mm

For the use of a Registered Medical Practitioner or a Hospital or a Laboratory only.

℞Crizotinib Capsules 250 mg

CRIZOKAST™

Each hard gelatin capsule contains:
Crizotinib 250 mg
Excipients qs
Approved colour used in empty capsule shell.

1.INDICATIONS AND USAGE
CRIZOKAST is indicated for the treatment of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) that is an a plastic lymphomakinase (ALK)-positive as detected by an FDA-approved test.

This indication is based on response rate. There are no data available demonstrating improvement in patient reported out comes or survival with CRIZOKAST.

2.DOSAGE AND ADMINISTRATION

Recommended Dosing
The recommended dose and schedule of CRIZOKAST is 250 mg taken orally twice daily. Continue treatment as long as the patient is deriving clinical benefit from therapy. Capsules should be swallowed whole. CRIZOKAST may be taken with or without food. If a dose of CRIZOKAST is missed, then it should be taken as soon as the patient remember unless it is less than 6 hours until the next dose, in which case the patient should not take the missed dose. Patients should not take 2 doses at the same time to make up for a missed dose.

Dose Modification
Dosing interruption and/or dose reduction may be required based on individual safety and tolerability. If dose reduction is necessary, then the dose of CRIZOKAST should be reduced to 200 mg taken orally twice daily. If further dose reduction is necessary, then reduce the dosage to 250 mg taken orally once daily based on individual safety and tolerability. Dose reduction guidelines for hematologic and non-hematologic toxicities are provided in Tables 1 and 2.

Table1: CRIZOKAST Dose Modification–Hematologic Toxicities[a]

CTCAE[b] Grade	CRIZOKAST Dosing
Grade3	With hold until recovery to Grade_>2, the resume at the same dose schedule
Grade4	With hold until recovery to Grade_>2, the resume at 200mg twice daily[c]

[a]Exceptly mphopenia(unlessassociatedwithclinicalevents,e.g.,opportunisticinfections).
[b]NCI Common Terminology Criteria for Adverse Events.
[c]Incase of recurrence, with hold until recovery toGrade≤2,thenresumeat250mgoncedaily.Permanently discontinue in case of Grade 4 recurrence.

Table2: CRIZOKAST Dose Modification–Non-Hematologic Toxicities

CTCAE Grade	CRIZOKAST Dosing
Grade 3or4 alanineamino transfer ase(ALT) or as partate amino transfer ase (AST) elevation with Grade ≤1 total bilirubin	With hold until recovery to Grade_>1, or baseline, the resume at 200mg twice daily[a]
Grade2,3or4ALTorASTelevationwith concurrent Grade 2, 3 or 4 total bilirubin elevation(in the absence of cholest as is or hemolysis)	Permanently discontinue
Any Grade pneumonitis[b]	Permanently discontinue
Grade3QTcprolongation	With hold until to recovery Grade_>1,the resume at 200mg twice daily[a]
Grade4QTcprolongation	Permanently discontinue

[a]In case of recurrence, with hold until recoverytoGrade≤1,then resume at 250 mg once daily. Permanently discontinue in case of further Grade 3 or 4 recurrence.
[b]Not attributable to NSCL Cprogression, other pulmonary disease, infection, orradiation effect.

Complete blood counts including differential white blood cell counts should be monitored monthly and as clinically indicated, with more frequent repeat testing if Grade 3 or 4 abnormalities are observed, or if fever or infection occurs. Liver function tests should be monitored monthly and as clinically indicated, with more frequent repeat testing if Grade 2, 3 or 4 abnormalities are observed.

3. DOSAGE FORMS AND STRENGTHS
250mgcapsules
Hard gelatin capsule, size 0, pink opaque cap and body,

200mgcapsules
Hard gelatin capsule, size1, white opaque body and pink opaque cap,

4. CONTRAINDICATIONS
None

5. WARNINGS AND PRECAUTIONS

Pneumonitis
CRIZOKAST has been associated with severe, life-threatening, or fatal treatment-related pneumonitis in clinical trials with a frequency of 4 in 255 (1.6%) patients across Studies A and B. All of these cases occurred within 2 months after the initiation of treatment. Patients should be monitored for pulmonary symptoms indicative of pneumonitis. Other causes of pneumonitis should be excluded. CRIZOKAST should be permanently discontinued in patients diagnosed with treatment-related pneumonitis

Hepatic Laboratory Abnormalities
Grade 3 or 4 A L Televation was observed in 7% of patients in Study Aandin 4% of patients in Study B. Grade 3 and 4 elevations were generally asymptomatic and reversible upon dosing interruption. Patients usually resumed treatment at a lower dose without recurrence; however, 3 patients from Study A (2%) and 1 patient from Study B (less than 1%) required permanent discontinuation from treatment. Concurrent televations in ALT greater than 3 x ULN and total bilirubin greater than 2 x ULN without elevated alkaline phosphatase were detected in 1/255 (less than 0.5%) of patients with available laboratory data across both studies. Liver function tests including ALT and total bilirubin should be monitored once a month and as clinically indicated, with more Frequent repeat testing for Grades 2,3 or 4 elevation in patients who develop transaminase elevation
[see Dosage and Administration and Adverse Reactions].

QT Interval Prolongation
Qtc prolongation has been observed. CRIZOKAST should be avoided in patients with congenital long QT syndrome. In patients with congestive heart failure, brady arrhythmias, electrolyte abnormalities, or who are taking medications that are known to prolong the QT interval, periodic monitoring with electrocardiograms (ECGs) and electrolytes should be considered. Permanently discontinue CRIZOKAST in patients who develop Grade 4 QTc prolongation. Withhold CRIZOKAST in patients who develop Grade 3 QTc prolongation until recovery to less than or equal to Grade 1, then resume CRIZOKAST at 200 mg twice daily. In case of recurrence of Grade 3 QTc prolongation, withhold CRIZOKAST until recovery to less than or equal to Grade 1, then resume CRIZOKAST at 250mg once daily. Permanently discontinue CRIZOKAST if Grade 3 QTC prolongation recurs
[see Dosage and Administration and Clinical Pharmacology].

ALK Testing
Detection of ALK-positive NSCLC using an FDA-approved test, indicated for this use, is necessary for selection of patients for treatment with CRIZOKAST *[see Clinical Studies (14)].*

Assessment for ALK-positive NSCLC should be performed by laboratories with demonstrated proficiency in the specific technology being utilized. Improper assay performance can lead to unreliable test results.

Refer to an FDA-approved test's package insert for in structions on the identification of patients eligible for treatment with CRIZOKAST.

Pregnancy
CRIZOKAST can cause fetal harm when administered to a pregnant woman based on its mechanism of action. In non clinical studies in rats, crizotinib was embryotoxic and fetotoxic at exposures similar to and above those observed in humans at the recommended clinical dose of 250 mg twice daily. There are no adequate and well-controlled studies in pregnant women using CRIZOKAST. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to a fetus *[see Use in Specific Populations].*

6. ADVERSE REACTIONS

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

In Studies A and B, patients with locally advanced or metastatic ALK- positive NSCLC received crizotinib 250 mg orally twice daily continuously. Among the 255 patients for whom data on Grade 1-4 adverse reactions are available, median exposure to study drug was 5.1 months in Study A and 7.8 months in Study B. Dosing interruptions occurred in 36% and 45% of patients in Studies A and B, and lasted greater than 2 weeks in 13% and 19% of patients in Studies A and B, respectively. Dose reductions occurred in 44% and 29% of patients in Studies A and B, respectively. The rates of treatment-related adverse events resulting in permanent discontinuation were 6% in Study A and 3% in Study B. The most common adverse reactions (≥25%) across both studies were vision disorder, nausea, diarrhea, vomiting, edema, and constipation. Grade 3-4 adverse reactions in at least 4% of patients in both studies included ALT increased and neutropenia.

Among the 397 patients for whom information on deaths and serious adverse reactions are available, deaths with in 28 days of the last dose of study drug occurred in 45 patients. Ten (2.5%) patients died with in 28 days of their first dose of study drug. Causes of death included disease progression (32 patients), respiratory events (9), and other (4). Respiratory causes of death included pneumonia (2), hypoxia (2), ARDS (1), dyspnea (1), pneumonitis (1), empyema (1), and pulmonary hemorrhage (1). Other causes of deaths included septic shock,

DIC, cardiovascular event, and death due to unknown cause (1each).Serious adverse events in greater than or equal to 2% of patients included pneumonia, dyspnea, and pulmonary embolism.

Table3 lists the common adverse reactions on Studies A and B in patients receiving CRIZOKAST.

Table3: Adverse Reactionsin≥10%of Patients with Locally Advanced or Metastatic ALK-Positive NSCLC on Studies A and B[1]

Adverse Event	Treatment Emergent N=255		Treatment Related N=255	
	All Grades n (%)	Grade3/4 n (%)	All Grades n (%)	Grade3/4 n (%)
Eye Disorders				
VisionDisorder[2]	163(64%)	0	159(62%)	0
Gastrointestinal Disorders				
Nausea Diarrhea	145(57%)	2 (<1%)	136(53%)	0
Vomiting	124(49%)	1 (<1%)	109(43%)	0
Constipation	116(45%)	3(1%)	101(40%)	0
EsophagealDisorder[3]	98(38%)	2 (<1%)	69(27%)	1 (<1%)
Abdominal Pain[4]	51(20%)	3(1%)	29(11%)	0
Stomatitis[5]	40(16%)	1 (<1%)	20(8%)	0
	27(11%)	1 (<1%)	15(6%)	1 (<1%)
General Disorders	97(38%)	2 (<1%)	72(28%)	0
Edema[6]Fatigue	80(31%)	6(2%)	51(20%)	4(2%)
Chest Pain/ Discomfort[7] Fever	30(12%)	1 (<1%)	3(1%)	0
	30(12%)	1 (<1%)	2 (<1%)	0
Infections and Infestations				
UpperRespiratoryInfection[8]	50(20%)	1 (<1%)	4(2%)	0
Investigations				
Alanine Amino transferase Increased As partate	38(15%)	17(7%)	34(13%)	14(5%)
Amino transferase Increased	29(11%)	7(3%)	24(9%)	5(2%)
Metabolism and Nutrition				
Decreased Appetite	69(27%)	3(1%)	49(19%)	0
Musculoskeletal				
Arthralgia Back	29(11%)	3(1%)	4(2%)	0
Pain	28(11%)	0	2 (<1%)	0
Nervous System Disorders				
Dizziness[9]	60(24%)	0	42(16%)	0
Neuropathy[10]	58(23%)	1 (<1%)	34(13%)	1 (<1%)
Headache	34(13%)	1 (<1%)	10(4%)	0
Dysgeusia	33(13%)	0	30(12%)	0
Psychiatric Disorders				
Insomnia	30(12%)	0	8(3%)	0
Respiratory Disorders				
Dyspnea	57(22%)	16(6%)	5(2%)	3(1%)
Cough	54(21%)	3(1%)	9(4%)	0
Skin Disorders				
Rash	41(16%)	0	25(10%)	0

[1]Study
Ansed CTCAE v 4.0 and Study BusedCTCAEv3.0.
[2]Includesdiplopia, photopsia, photophobia, visionblurred, visual field defect, visual impairment, vitreous floaters, visual brightness, and visual acuity reduced.
[3]Includesdyspepsia, dysphagia, epigastric discomfort/ pain/ burning, esophagitis, esophageal obstruction/pain/spasm/ulcer, gastro esophageal reflux, odynophagia, and reflux esophagitis.
[4]Includesabdominaldiscomfort, abdominal pain, abdominal pain upper and abdominal tenderness.
[5]Includesmouthulceration, glossodynia, glossitis, cheilitis, mucosal inflammation, or pharyngeal pain/ discomfort, oral pain, and stomatitis.

[6] include edema, edema localized, and peripheral edema.
[7] include chest pain, chest discomfort, and musculoskeletal chestpain.
[8]Includes nasopharyngitis, rhinitis, pharyngitis, and upper respiratory tractinfection.
[9]Includes balance disorder, dizziness, and presyncope.
[10]Includesburningsensation, dysesthesia, hyperesthesia, hypoesthesia, neuralgia, paresthesia, peripheral neuropathy, peripheral motor neuropathy, and peripheral sensory neuropathy.

Vision disorders including visual impairment, photopsia, vision blurred, vitreous floaters, photophobia, and diplopia were reported in 159 (62%) patients in clinical trials. These events generally started within two weeks of drug administration. Ophthalmological evaluation should be considered, particularly if patients experience photopsia or experience new or increased vitreous floaters. Severe or worsening vitreous floaters and/or photopsia could also be signs of retinal hole or pending retinal detachment. Caution should be exercised when driving or operating machinery by patients who experience vision disorder *[see Patient Counseling Information].*

Neuropathy as defined in Table 3 and attributed to study drug by the investigator was reported in 34 (13%) patients. While most events were Grade 1, Grade 2 motor neuropathy and Grade 3 peripheral neuropathy were reported in 1patient each. Dizziness and dysgeusia were also very commonly reported in these studies, but were all Grade 1 or 2 in severity.

Bradycardia has been reportedin12 (5%) patients treated with CRIZOKAST. All of these cases were Grade1or2 in severity.

Complex renalcysts have been reported in 2(1%) patients treated with CRIZOKAST. There were no reports of abnormal urinalyses or renal impairment in these cases.

Laboratory Abnormalities

Grade3or4neutropenia, thrombocytopenia, and lymphopenia were seen in 5.2%, 0.4%, and 11.4% of patients, respectively.

7. DRUG INTERACTIONS

Drugs That May Increase Crizotinib Plasma Concentrations

Co administration of crizotinib with strong CYP3A inhibitors increases crizotinib plasma concentrations *[see Clinical Pharmacology]*. The concomitant use of strong CYP3A in hibitors, including but not limited to at azanavir, clarithromycin, indinavir, it raconazole, ketoconazole, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, troleandomycin, and voriconazole, should be avoided. Grapefruit or grapefruit juice may also increase plasma concentrations of crizotinib and should be avoided. Caution should be exercised with concomitant use of moderate CYP3A inhibitors.

Drugs That May Decrease Crizotinib Plasma Concentrations

Co administration of crizotinib with strong CYP3 A inducers decreases crizotinib plasma concentrations *[see Clinical Pharmacology (12.3)]*. The concurrent use of strong CYP3A inducers, including but not limited to carbamazepine, phenobarbital, phenytoin, rifabutin, rifampin, and St. John's Wort, should be avoided.

Drugs Whose Plasma Concentrations May Be Altered By Crizotinib

Crizotinib in hibits CYP3A both *invitro* and *invivo [see Clinical Pharmacology].* Dose reduction may be needed for co administered drugs that are predominantly metabolized by CYP3A. Co administration of crizotinib with CYP3A substrates with narrow therapeutic indices, including but not limited to alfentanil, cyclosporine, dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, sirolimus, and tacrolimus, should be avoided.

8. USE IN SPECIFIC POPULATIONS

Pregnancy

Pregnancy Category D *[see " Warnings and Precautions"]*

CRIZOKAST can cause fetal harm when administered to a pregnant woman based on its mechanism of action. There are no adequate and well-controlled studies of CRIZOKAST in pregnant women. In nonclinical studies in rats, crizotinib was embryotoxic and fetotoxic at exposures similar to and above those observed in humans at the recommended clinical dose of 250 mg twice daily. Crizotinib was administered to pregnant rats and rabbits during organogenes is to study the effects on embryo-fetal development. Post implantation loss was increased at doses ≥ 50 mg/kg/day (approximately 1.2 times the AUC at the recommended human dose) in rats. No teratogenic effects were observed in rats at doses up to the maternally toxic dose of 200 mg/kg/day (approximately 5 times the AUC at the recommended human dose) or in rabbits at doses of up to 60mg/kg/day (approximately 3 times the AUC at the recommended human dose), though fetal body weights were reduced at these doses.

Women of child bearing potential should be advised to avoid becoming pregnant while receiving CRIZOKAST. Women of child bearing potential who are receiving this drug, or partners of women of child bearing potential receiving this drug, should use adequate contraceptive methods during therapy and for at least 90 days after completing therapy. If this drug is used during pregnancy, or if the patient or their partner becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to a fetus.

Nursing Mothers

It is not known whether CRIZOKAST is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from CRIZOKAST, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use

The safety and efficacy of CRIZOKAST in pediatric patients has not been established. Decreased bone formation in growing long bones was observed in immature rats at 150 mg/kg/day following once daily dosing for 28 days (approximately 10 times the AUC in adult patients at the recommended human dose). Other toxicities of potential concern to pediatric patients have not been evaluated in juvenile animals.

Geriatric Use

Clinical studies of CRIZOKAST did not include sufficient numbers of patients aged 65 and older to determine whether they respond differently from younger patients.Of the136 patients in StudyA,19 (14%)were 65years or older. Of the 119 patients in Study B, 16 (13%) were 65 years or older.

Hepatic Impairment

CRIZOKAST has not been studied in patients with hepatic impairment. As crizotinib is extensively metabolized in the liver, hepatic impairment is likely to increase plasma crizotinib concentrations. Clinical studies excluded patients with AST or ALT greater than 2.5 x ULN, or greater than 5 x ULN, if due to liver metastases. Patients with total bilirubin greater than 1.5 x ULN were also excluded. Treatment with CRIZOKAST should be used with caution in patients with hepatic impairment *[see Clinical Pharmacology].*

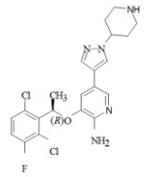
Renal Impairment

No starting dose adjustment is needed for patients with mild (creatinine clearance[CLcr] 60 to 90mL/min)and moderate renal impairment (CLcr 30 to 60 mL/min), as steady-state trough concentrations in these two groups were similar to those in patients with normal renal function (CLcr greater than 90 mL/min) in Study B. The potential need for starting dose adjustment in patients with severe renal impairment cannot be determined, as clinical and pharmacokinetic data were available for only one patient. In addition, no data are available for patients with end-stage renal disease. Therefore, caution should be used in patients with severe renal Impairment (CL crless than 30mL/min) or patients with end-stager enaldisease *[see Clinical Pharmacology].*

9. OVER DOSAGE
There have been no known cases of CRIZOKAST overdose. Treatment of over dose with CRIZOKAST should consist of general supportive measures. There is no antidote for CRIZOKAST.

10. DESCRIPTION
CRIZOKAST (crizotinib) is an oral receptor tyrosine kinase inhibitor. The molecular formula for crizotinib is $C_{21}H_{22}Cl_2FN_5O$. The molecular weight is 450.34 Daltons. Crizotinib is described chemically as (*R*)-3-[1-(2,6- Dichloro- 3-fluorophenyl) ethoxy]-5-[1- (piperidin-4-yl)-1*H*-pyrazol-4-yl]pyridin-2-amine.

The chemical structure of crizotinib is shown below:



Crizotinib is a white to pale-yellow powder with a pKa of 9.4(piperidiniumcation) and 5.6 (pyridiniumcation). The solubility of crizotinib in aqueous media decreases over the range pH 1.6 to pH 8.2 from greater than 10 mg/mL to less than 0.1 mg/mL. The log of the distribution coefficient (octanol/water) at pH 7.4 is 1.65.
CRIZOKAST capsules are supplied as printed hard-shell capsules containing 250 mg or 200 mg of crizotinib to gether with colloidalsilicondioxide, microcrystalline cellulose, anhydrous dibasic calc iumphosphate, sodium starch glycolate, magnesium stearate, and hard gelatin capsule shells as inactive ingredients.
The pink opaque capsule shell components contain gelatin, titanium dioxide, and red iron oxide. The white opaque capsule shell components contain gelatin, and titanium dioxide. The printing ink contains shellac, propylene glycol, strong ammonia solution, potassium hydroxide, and black iron oxide.

12. CLINICAL PHARMACOLOGY

Mechanism of Action

Crizotinib is an inhibitor of receptor tyrosine kinases including ALK, Hepatocyte Growth Factor Receptor (HGFR, c-Met), and Recepteur d'Origine Nantais (RON). Translocations can affect the ALK gene resulting in the expression of oncogenic fusion proteins. The formation of ALK fusion proteins results in activation and dysregulation of the gene's expression and signaling which can contribute to increased cell proliferation and survival in tumors expressing these proteins. Crizotinib demonstrated concentration-dependent inhibition of ALKandc-Met phosphorylation in cell-based assays using tumor cell lines and demonstrated antitumor activity in mice bearing tumor xenografts that expressed EML4- or NPM-ALK fusion proteins or c-Met.

Pharmacokinetics

Absorption

Following oral single-dose administration, crizotinib was absorbed with median time to achieve peak concentration of4 to 6 hours. Following crizotinib 250mg twice daily, steady state was reached within 15 days and remained stable, with a median accumulation ratio of 4.8. Steady state systemic exposure (C_{min} and AUC) appeared to increase in a greater than and is proportional manner over the dose range of 200-300mg twice daily.
The mean absolute bioavailability of crizotinib was 43% (range:32%to66%)following the administration of a single 250 mg oral dose.
A high – fat meal reduced crizotinib AUC_{inf} and C_{max} by approximately1 4%. CRIZOKAST can be administered with or without food *[see Dosage and Administration].*

Distribution

The geometric mean volume o distribution (Vss) of crizotinib was 1,772 L following in travenous administration of a 50 mg dose, indicating extensive distribution into tissues from the plasma.

Binding of crizotinib to human plasma proteins *invitro* is 91% and is independent of drug concentration. *In vitro* studies suggested that crizotinib is a substrate for P-glycoprotein (P-gp). The blood-to-plasma concentration ratio is approximately 1.

Metabolism

In vitro studies demonstrated that crizotinib is predominantly metabolized by CYP3A4/5. The primary metaboli pathways in humans were oxidation of the piperidine ring to crizotinib lactamand *O*-dealkylation, with subsequent Phase 2 conjugation of *O*-dealkylated metabolites.

Invitro studies in human live r micro somes demonstrated that crizotinib is a time-dependent in hibitor of CYP3A.

Elimination

Following single doses of crizotinib, the plasma terminal half-life of crizotinib was 42 hours in patients.
Following the administration of a single 250mg radio labeled crizotinib dose to healthy subjects, 63% and 22% of the administered dose was recovered in feces and urine, respectively. Unchanged crizotinib represented approximately 53% and 2.3% of the administered dose in feces and urine, respectively.
Then apparent clearance (CL/F) of crizotinib was lower at steady state (60L/hr) after 250mg twice daily than that after a single 250 mg oral dose (100 L/hr), which was likely due to auto inhibition of CYP3A by crizotinib after multiple dosing.

Drug Interactions

Co administration of Crizotinib and CYP3A Substrates
Crizotinib in hibits CYP3A both *invitro* and *invivo*. Co administration of crizotinib (250 mg twice dailyfor28 days) in patients resulted in a geometric mean oral midazolam AUC that was 3.7-fold that observed when midazolam was administered alone, suggesting that crizotinib is a moderate inhibitor of CYP3A *[see Drug Interactions].*

Co administration of Crizotinib and CYP3A Inhibitors
Co administration of a single 150 mg oral dose of crizotinib in the presence of ketoconazole (200 mg twice daily), a strong CYP3A inhibitor, resulted in increases in crizotinib systemic exposure, with crizotinib AUC_{inf} and C_{max} values that were approximately 3.2-fold and 1.4 fold, respectively, those seen when crizotinib was administered alone. However, the magnitude of effect of CYP3A inhibitor son steady state crizotinib exposure has not been evaluated
[see Drug Interactions].

Co administration of Crizotinib and CYP3A Inducers
Co administration of a single 250 mg crizotinib dose with rifamp in (600 mg QD), a strong CYP3A inducer, decreased crizotinib AUC_{inf} and C_{max} by 82% and 69%, respectively, compared to crizotinib alone. However, the effect of CYP3A inducers on steady - state crizotinib exposure as not been evaluated *[see Drug Interactions].*

Co administration of Crizotinib and Antacids
The aqueous solubility of crizotinib is pH dependent, with higher pH resulting in lower solubility. Drugs that elevate the gastric pH(such as proton pump in hibitors,H_2 blockers, orantacids) may decrease the solubility of crizotinib and subsequently reduce its bio availability.
However, no formal studies have been conducted.

Co administration with Other CYP Substrates
In vitro studies indicated that clinical drug-drug interactions are unlikely to occur as a result of crizotinib- mediated inhibition of the metabolism of substrates for CYP1A2, CYP2B6, CYP2C8,CYP2C9, CYP2C19, or CYP2D6.

An *invitro* study in human hepatocytes indicated that clinical drug-drug interactions are unlikely to occur as a result of crizotinib- mediated induction of the metabolism of substrates for CYP1A2 or CYP3A.

Co administration with Substrates of Transporters
Crizotinib is an inhibitor of P-glycoprotein (P-gp) *invitro*. Therefore, crizotinib may have the potential to increase plasma concentrations of coadministered substrates of P-gp. *Invitro,* crizotinib did not inhibit the human hepatic up take transport proteins OATP1B1 or OATP1B3 at therapeutic concentrations. Therefore, clinical drug-drug interactions are unlikely to occur as a result of crizotinib - mediated inhibition of the hepatic uptake of substrates for these transporters.

Pharmacokinetics in Special Populations

Hepatic Impairment: As crizotinib is extensively metabolized in the liver, hepatic impairment is likely to increase plasma crizotinib concentrations. However, CRIZOKAST has not been studied in patients with hepatic impairment. Clinical studies excluded patients with ALT or AST greater than 2.5 x ULN or greater than 5 x ULN if due to liver meta stases. Patients withtot a lbilirub in greater than 1.5 x ULN were also excluded *[see Use in Specific Populations].*

Renal Impairment: No dedicated renal impairment trial for CRIZOKAST has been conducted. In Study B, steady- state trough concentrations in patients with mild (CL cr 60 to 90 mL / min, N=47)and moderate renal impairment (CLcr 30 to 60 mL/min, N=27) were similar to those in patients with normal renal function (Clcr greater than 90 mL/ min, N=33). Limited data (N=1) are available in patients with severe renal impairment, and no data are available in patients with end-stage renal disease *[see Use in Specific Populations].*

Ethnicity: After 250mg twice daily dosing, steady- state crizotinib C_{max} and AUC in Asian patients were 1.57- and 1.50-fold those seen in non-Asian patients, respectively.

Cardiac Electrophysiology

The QT interval prolongation potential of crizotinib was assessed in all patients who received CRIZOKAST 250 mg twice daily. Serial ECGs in triplicate were collected following a single dose and at steady state to evaluate the effect of crizotinib on Qt intervals. Four of 308 patients (1.3%) were found to have QTcF (corrected QT by the Fridericia method) greater than or equal to 500 msec, and 10 of 289 patients (3.5%) had an increase from base line QTcF greater than or equal to 60 m sec by automated machine-read evaluation of ECG.A pharmacokinetic/ pharmacodynamic analysis suggested a concentration-dependent increase in QTcF *[see Warnings and Precautions].*

13. NONCLINICAL TOXICOLOGY

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity studies with crizotinib have not been conducted.
Crizotinib was genotoxic in an *invitro* micro nucleus assay in Chinese Hamster Ovary cultures, inan *in vitro* Human lymphocyte chromo some a berration assay, and in *invivo* rat bone marrow micronucleus assays. Crizotinib was not mutagenic *in vitro* in the bacterial reverse mutation (Ames) assay.
No specific studies with crizotinib have been conducted in animals to evaluate the effect on fertility; however, crizotinib is considered to have the potential to impair reproductive function and fertility in humans based on findings in repeat-dose toxicity studies in the rat. Findings observed in the male reproductive tract included testicular pachytene spermatocyte degeneration in rats given greater than or equal to 50 mg/kg/day for 28 days (greater than 3 times the AUC at the recommended human dose). Findings observed in the female reproductive tract included single cell necrosis of ovarian follicle so far at given 500 mg/kg/day (approximately 10 times the recommended human daily dose on a mg/m^2 basis) for 3 days.

14. CLINICALSTUDIES

The use of single-agent CRIZOKAST in the treatment of locally advanced or metastatic ALK positive NSCLC was investigated in 2multi-center,single studies (Studies A and B). Patients enrolled in to these studies had received prior systemic therapy, with the exception of 15 patients in Study B who had no prior systemic treatment for locally advanced or meta static disease. In Study A, ALK-positive NSCLC was identified using the Vys is ALK Break-Apart FISH Probe Kit. In Study B, ALK-positive NSCLC was identified using a number of local clinical trial assays.
The primary efficacy endpoint in both studies was Objective Response Rate (ORR) according to Response Evaluation Criteria in Solid Tumors (RECIST).
Response was evaluated by the investigator and by an independent radiology review panel. Duration of Response (DR) was also evaluated. Patients received
250mg of CRIZOKAST
orally twice daily. Demographic and disease characteristics for Studies A and B are provided in Table 4.

Table4: Demo graphic and Disease Characteristics in Studies A and B

Characteristics	Study A N=136	Study B N=119
Sex, n (%)		
Male	64(47)	59(50)
Female	72(53)	60(50)
Age(years)		
Median(range)	52(29-82)	51(21-79)
Race, n (%)		
White	87(64)	74(62)
Black	5(4)	3(3)
Asian	43(32)	34(29)
Other	1(1)	8(7)
ECOGP Satbaseline, n(%)		
0	37(27)	41(35)
1	74(54)	63(53)
2–3*	25(18)	15(13)
Smoking status, n (%)		
Never smoked	92(68)	86(72)
Former smoker	39(29)	32(27)
Current smoker	5(4)	1(1)
Disease stage n (%)		
Locally advanced	9(7)	5(4)
Metastatic	127(93)	114(96)
Histological classification (%)		
Adenocarcinoma	130(96)	116(98)
Large cell carcinoma	1(1)	1(1)
Squamous cell carcinoma	0	1(1)
Adenosquamouscarcinoma	3(2)	0
Other	2(2)	1(1)
Prior systemic therapy for locally advance dormetastatic disease -- number of regimens, n (%)		
0	0	15(13)
1	13(10)	34(29)
2	37(27)	20(17)
3	37(27)	17(14)
≥4	49(36)	33(28)

*Includes 1 patient with an ECOGPS of 1at screening but was 3 at baseline.

One hundred thirty-six patients with locally advanced or metastatic ALK-positive NSCLC from Study A were analyzed at the time of data cutoff. The median duration of treatment was 22 weeks. Based on investigator assessments, there was1complete and 67 partial responses for an ORR of 50% (95% CI: 42%, 59%). Seventy- nine percent of objective tumor responses were achieved during the first 8 weeks of treatment. The median response duration was 41.9 weeks.

One hundred nineteen patients with locally advanced or metastatic ALK-positive NSCLC were enrolled into Study B at the time of data cutoff. The median duration of treatment was 32 weeks. Based on investigator assessments, there were 2complete and 69 partial responses for an ORR of 61% (95% CI: 52%, 70%).Fifty-five percent of objective tumor responses were achieved during the first 8 weeks of treatment. The median response duration was 48.1 weeks.

Efficacy data from Studies A and B are provided in Table 5.

Table5: Locally Advanced or Metastatic ALK-Positive NSCLC Efficacy Results from Studies A and B[a]

Efficacy Parameter	Study A N=136	Study B N=119
ORR (CR+PR)[b] [%(95%CI)]	50% (42%,59%)	61% (52%, 70%)
Number of Responders	68	71
Duration of Response[c] [Median(range)weeks]	41.9(6.1+,42.1+)	48.1(4.1+,76.6+)

[a] Response as assessed by the Investigator.
[b] One patient was note valuable for response in Study A; 3patients were not evaluable for response in Study B.
[c] Preliminary yes timate using Kaplan-Meier method.
+Censored values

15. HOW SUPPLIED /STORAGE AND HANDLING

250mg capsules
Hard gelatin capsule with pink opaque cap and body, available in: Bottles of 60 capsules:
200mg capsules
Hard gelatin capsule with pink opaque cap and white opaque body, available in: Bottles of 60 capsules:

Store at room temperature 20°C to 25°C (68° to 77°F); excursions permitted between 15° to 30°C (59° to 86°F).

16. PATIENT COUNSELING INFORMATION

See FDA-Approved Patient Labeling.

Gastrointestinal Effects

Patients should be informed that nausea, diarrhea, vomiting, and constipation were the most commonly reported gastrointestinal adverse events occurring in patients who received CRIZOKAST. Supportive care for gastrointestinal adverse events requiring treatment may include standard anti-emetic and/or anti-diarrheal or laxative medications *[see Adverse Reactions].*

Visual Effects

Patients should be informed that visual changes such as perceived flashes of light, blurry vision, light sensitivity, and floaters were commonly reported adverse events. These events began most commonly during the first two weeks of treatment. Patients should be advised to report flashes or floaters to their physicians.

Effects on Ability to Drive and Use Machines

No studies on the effect of CRIZOKAST on the ability to drive and use machines have been performed. However, caution should be exercised when driving or operating machinery by patients who experience vision disorder, dizziness, or fatigue while taking CRIZOKAST.

Concomitant Medications

Patients should be advised to inform their health care providers of all concomitant medications, including prescription medicines, over-the-counter drugs, vitamins, and herbal products *[see Drug Interactions].*

Instructions for Taking CRIZOKAST

Patients should be advised to take CRIZOKAST exactly as prescribed, not to change their dose or to stop taking CRIZOKAST unless they are told to do so by their doctor. CRIZOKAST may be taken with or without food.
CRIZOKAST capsules should be swallowed whole.

Patients should be instructed to keep CRIZOKAST in the original container. Patients should not crush, dissolve, or open capsules.

Patients should avoid grape fruit or grape fruit juice while taking CRIZOKAST.

If a patient misses a dose, the patient should be advised to take it as soon as they remember unless it is less than 6 hours until the next dose, in which case they should not take the missed dose. Patients should not take 2 doses at the same time to make up for a missed dose.

Pregnancy and Nursing

Patients of child bearing potential must be told to use adequate contraceptive methods during therapy and for at least 90 days after completing therapy. Patients should be advised to inform their doctor if they or their partners are pregnant or think they may be pregnant. Patients should also be advised not to breastfeed while taking CRIZOKAST.

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