Therapy Management Guide

For adult patients with *KRAS G12C*–mutated locally advanced or metastatic non-small cell lung cancer (NSCLC) as determined by an FDA-approved test, who have received at least one prior systemic therapy.

INDICATION

KRAZATI, as a single-agent, is indicated for the treatment of adult patients with KRAS G12C-mutated locally advanced or metastatic non-small cell lung cancer (NSCLC) as determined by an FDA-approved test, who have received at least one prior systemic therapy.

This indication is approved under accelerated approval based on objective response rate (ORR) and duration of response (DOR). Continued approval for this indication may be contingent upon verification and description of a clinical benefit in a confirmatory trial.

SELECT IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

Gastrointestinal Adverse Reactions

- KRAZATI can cause severe gastrointestinal adverse reactions
- Monitor and manage patients using supportive care, including antidiarrheals, antiemetics, or fluid replacement, as indicated. Withhold, reduce the dose, or permanently discontinue KRAZATI based on severity

Please see additional Important Safety Information on pages 24–25 and Full Prescribing Information.

KRAZATI® (adagrasib) 200 mg TABLETS

KRAZATI, as a single-agent, is indicated for the treatment of adult patients with *KRAS G12C*-mutated locally advanced or metastatic non-small cell lung cancer (NSCLC) as determined by an FDA-approved test, who have received at least one prior systemic therapy.

This indication is approved under accelerated approval based on objective response rate (ORR) and duration of response (DOR). Continued approval for this indication may be contingent upon verification and description of a clinical benefit in a confirmatory trial.

This Therapy Management Guide presents each topic in a clear format that is easy to navigate and access during a busy patient visit, and helps you manage your patients throughout their treatment journey.

This Therapy Management Guide does not include all of the information needed to prescribe KRAZATI safely and effectively.

See Full Prescribing Information for KRAZATI.

SELECT IMPORTANT SAFETY INFORMATION

QTc Interval Prolongation

- KRAZATI can cause QTc interval prolongation, which can increase the risk for ventricular tachyarrhythmias (eg, torsades de pointes) or sudden death
- Avoid concomitant use of KRAZATI with other products with a known potential to prolong the QTc interval. Avoid use of KRAZATI in patients with congenital long QT syndrome and in patients with concurrent QTc prolongation
- Monitor ECGs and electrolytes, particularly potassium and magnesium, prior to starting KRAZATI, during concomitant use, and as clinically indicated in patients with congestive heart failure, bradyarrhythmias, electrolyte abnormalities, and in patients who are unable to avoid concomitant medications that are known to prolong the QT interval. Correct electrolyte abnormalities. Withhold, reduce the dose, or permanently discontinue KRAZATI, depending on severity

Please see additional Important Safety Information on pages 24–25 and Full Prescribing Information.

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Questions?
CLICK HERE TO CONNECT WITH US

GI=gastrointestinal; ILD=interstitial lung disease.

KRAZATI Recommended Dosage: 600 mg BID[1]

3 TABLETS ORALLY | 2X DAILY

Until disease progression or unacceptable toxicity

2x

AM **Take (3) 200 mg tablets by mouth in the morning**

PM **Take (3) 200 mg tablets by mouth at night**

How Large Is One Tablet of KRAZATI?

Pea 1 cm

Actual size 1.5 cm

Peanut 2 cm

- Available as immediate release tablets
- Advise patients to take KRAZATI at the same time every day with or without food
- KRAZATI tablets should be swallowed whole (not chewed, crushed, or split)
- If a patient misses a dose by more than 4 hours or if vomiting occurs, they should resume dosing at the next scheduled time
- There are no restrictions for use of PPIs or H_2-receptor antagonists in the KRAZATI Prescribing Information

BID=twice daily; PPI=proton pump inhibitor.

Please see Important Safety Information on pages 24–25 and Full Prescribing Information.

Monitoring Your Patient[1]

Patients may experience adverse reactions (ARs) when they take KRAZATI. Careful monitoring can provide important information for managing treatment.

MONITORING PRIOR TO AND THROUGHOUT TREATMENT

Warnings and Precautions	Monitoring
• Gastrointestinal ARs	• Monitor and manage patients using supportive care, including antidiarrheals, antiemetics, or fluid replacement, as indicated
• QTc Interval Prolongation	• Monitor ECGs and electrolytes prior to starting KRAZATI, during concomitant use, and as clinically indicated in patients with congestive heart failure, bradyarrhythmias, electrolyte abnormalities, and in patients who are unable to avoid concomitant medications that are known to prolong the QT interval
• Hepatotoxicity	• Monitor liver laboratory tests (AST, ALT, alkaline phosphatase and total bilirubin) prior to the start of KRAZATI and monthly for 3 months or as clinically indicated, with more frequent testing in patients who develop transaminase elevations
• ILD/Pneumonitis	• Monitor patients for new or worsening respiratory symptoms indicative of ILD/pneumonitis (eg, dyspnea, cough, fever) during treatment with KRAZATI

ALT=alanine aminotransferase; AST=aspartate aminotransferase; ECG=electrocardiogram; ILD=interstitial lung disease.

Please see Important Safety Information on pages 24–25 and Full Prescribing Information.

Patient Discussion Points[1]

GI ADVERSE REACTIONS (ARs)

- Advise patients that KRAZATI can cause severe GI ARs and to contact their healthcare provider for signs or symptoms of severe or persistent GI ARs

QTc INTERVAL PROLONGATION

- Advise patients that KRAZATI can cause QTc interval prolongation and to contact their healthcare provider for signs or symptoms of arrhythmias

HEPATOTOXICITY

- Advise patients that KRAZATI can cause hepatotoxicity and to immediately contact their healthcare provider for signs or symptoms of liver dysfunction

ILD/PNEUMONITIS

- Advise patients that KRAZATI can cause ILD/pneumonitis and to contact their healthcare provider for immediately new or worsening respiratory symptoms

GI=gastrointestinal; ILD=interstitial lung disease.

Please see Important Safety Information on pages 24–25 and Full Prescribing Information.

Patient Discussion Points (cont'd)[1]

DRUG INTERACTIONS

- Advise patients to inform their healthcare providers of all concomitant medications, including prescription medicines, over-the-counter drugs, vitamins, and herbal products

MISSED DOSE

- If a dose of KRAZATI is missed by greater than 4 hours, resume dosing at the next scheduled time

LACTATION

- Advise women not to breastfeed during treatment with KRAZATI and for 1 week after the last dose

INFERTILITY

- Inform patients that KRAZATI may cause infertility

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

Adverse Reactions (ARs)[1]

KRAZATI was evaluated in a pooled patient population as a single agent at 600 mg orally twice daily in 366 patients with NSCLC and other solid tumors in KRYSTAL-1 and KRYSTAL-12. In KRYSTAL-1, 116 patients with *KRAS G12C*-mutated advanced NSCLC received KRAZATI 600 mg orally BID.

ADVERSE REACTIONS (≥20%) IN PATIENTS WITH *KRAS G12C*–MUTATED NSCLC WHO RECEIVED KRAZATI IN KRYSTAL-1[1,2]

Adverse Reaction	KRAZATI (N=116)			
	Grade 1 (%)	Grade 2 (%)	Grade 3 (%)	Grade 4 (%)
GI Disorders				
Diarrhea*	54.3	14.7	0.9	0
Nausea	40.5	24.1	4.3	0
Vomiting*	39.7	15.5	0.9	0
Constipation	18.1	4.3	0	0
Abdominal pain*	12.1	8.6	0	0
General Disorders and Administration Site Conditions				
Fatigue*	22.4	29.3	6.9	0
Edema*	26.7	5.2	0	0
Respiratory				
Dyspnea*	9.5	15.5	8.6	1.7
Cough*	15.5	7.8	0.9	0
Musculoskeletal and Connective Tissue Disorders				
Musculoskeletal pain*	19.8	14.7	6.9	0
Hepatobiliary Disorders				
Hepatotoxicity*†	12.9	13.8	9.5	0.9

*Grouped term.

†Hepatotoxicity includes mixed liver injury, blood alkaline phosphatase increased, alanine aminotransferase increased, aspartate aminotransferase increased, liver function test increased, blood bilirubin increased, and bilirubin conjugated increased.

BID=twice-daily; GI=gastrointestinal; NSCLC=non-small cell lung cancer.

Adverse Reaction (Continued)	KRAZATI (N=116)			
	Grade 1 (%)	Grade 2 (%)	Grade 3 (%)	Grade 4 (%)
Renal and Urinary Disorders				
Renal impairment*‡	23.3	6.9	6.0	0
Metabolism and Nutrition Disorders				
Decreased appetite	13.8	12.1	4.3	0
Infections and Infestations				
Pneumonia*	1.7	3.4	16.4	0.9
Nervous System Disorders				
Dizziness*	18.1	4.3	0.9	0
Cardiac Disorders				
Electrocardiogram QT prolonged	9.5	4.3	6.0	0

*Grouped term.
‡Renal impairment includes acute kidney injury and increased blood creatinine.

Serious ARs were reported in 57% of patients receiving KRAZATI. Fatal ARs occurred in 11% of patients. Serious adverse reactions in ≥2% of patients were pneumonia, dyspnea, renal impairment, sepsis, hypoxia, pleural effusion, respiratory failure, anemia, cardiac failure, hyponatremia, hypotension, muscular weakness, pyrexia, dehydration, diarrhea, mental status changes, pulmonary embolism, and pulmonary hemorrhage. Fatal adverse reactions in patients were pneumonia, respiratory failure, sudden death, cardiac failure, cerebrovascular accident, mental status change, pulmonary embolism, and pulmonary hemorrhage.

Permanent discontinuation of KRAZATI due to an AR occurred in 15/116 patients

Please see Important Safety Information on pages 24–25 and Full Prescribing Information.

Laboratory Abnormalities[1]

SELECT LABORATORY ABNORMALITIES OCCURRING (≥25%) THAT WORSENED FROM BASELINE IN PATIENTS WITH *KRAS G12C*-MUTATED NSCLC WHO RECEIVED KRAZATI IN KRYSTAL-1

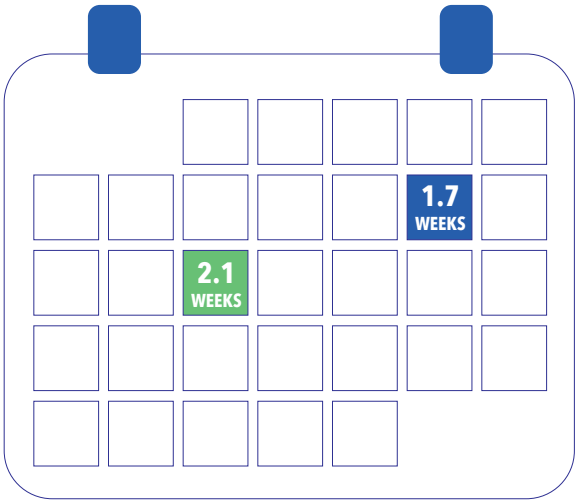
Laboratory Abnormality	KRAZATI*	
	All Grades (%)	Grade 3 or 4 (%)
Hematology		
Decreased lymphocytes	64	25
Decreased hemoglobin	51	8
Decreased platelets	27	0
Chemistry		
Increased aspartate aminotransferase	52	6
Decreased sodium	52	8
Increased creatinine	50	0
Decreased albumin	50	0.9
Increased alanine aminotransferase	46	5
Increased lipase	35	1.8
Decreased magnesium	26	0
Decreased potassium	26	3.5

*Denominator used to calculate the rate varied from 106 to 113 based on the number of patients with a baseline value and at least one post-treatment value.

NSCLC=non-small cell lung cancer.

Time to Onset and Resolution of Select Adverse Reactions (ARs)[3]

Overall, 92% of patients with GI ARs (diarrhea, nausea, and vomiting) reported the initial event within the first 6 weeks.



- The median time to resolution after an initial occurrence was **1.7 weeks** for increased ALT and AST levels*
- The median time to resolution after an initial occurrence was **2.1 weeks** for GI ARs†

Monitoring and support for patients is important in **the first 6 weeks** and throughout treatment

*The range for the time to resolution after an initial occurrence was 0.3 to 15.1 weeks for increased ALT and AST levels.

†The range for the time to resolution after an initial occurrence was 0.1 to 50.1 weeks for GI ARs.

ALT=alanine aminotransferase; AST=aspartate aminotransferase; GI=gastrointestinal.

Please see Important Safety Information on pages 24–25 and Full Prescribing Information.

Dosage Modifications for Adverse Reactions (ARs)[1]

DOSAGE REDUCTIONS

Recommended dosage: 600 mg orally, twice daily

1 FIRST DOSE REDUCTION
400 MG TWICE DAILY
(4) 200 mg tablets

2 SECOND DOSE REDUCTION
600 MG ONCE DAILY
(3) 200 mg tablets

For more information about dosage modifications for ARs, refer to the KRAZATI Prescribing Information and Therapy Management Guide.

DOSAGE MODIFICATIONS IN KRYSTAL-1 (COHORT A) N=116

Dosage interruptions due to an AR occurred in 77% of patients

- ARs requiring dosage interruption in ≥2% of patients included nausea, hepatotoxicity, fatigue, vomiting, pneumonia, renal impairment, diarrhea, QTc interval prolongation, anemia, dyspnea, increased lipase, decreased appetite, dizziness, hyponatremia, muscular weakness, increased amylase, pneumonitis, sepsis, and decreased weight

Dosage reductions due to an AR occurred in 28% of patients

- ARs requiring dosage reductions in ≥2% of patients included hepatotoxicity, fatigue, nausea, diarrhea, vomiting, and renal impairment

13% of patients discontinued due to an AR

Dosage modifications can help patients continue on therapy without the immediate need for a new prescription

Dosage Modifications for Adverse Reactions (ARs)[1]

Refer to the table below for recommended dosage modifications for ARs.

Adverse Reaction	Severity*	Dosage Modification
Nausea or vomiting despite appropriate supportive care (including antiemetic therapy) **Diarrhea despite appropriate supportive care** (including antidiarrheal therapy)	Grade 3 or 4	• **Withhold** KRAZATI until recovery to ≤ Grade 1 or return to baseline. • **Resume** KRAZATI at the next lower dose level.
QTc Interval Prolongation	QTc absolute value greater than 500 ms or greater than an increase of 60 ms from baseline	• **Withhold** KRAZATI until QTc interval less than 481 ms or return to baseline. • **Resume** KRAZATI at the next lower dose level.
	Torsade de pointes, polymorphic ventricular tachycardia or signs of symptoms of serious or life-threatening arrhythmia	• **Permanently discontinue** KRAZATI.
Hepatotoxicity	Grade 2 AST or ALT	• **Decrease** KRAZATI to the next lower dose level.
	Grade 3 or 4 AST or ALT	• **Withhold** KRAZATI until recovery to ≤ Grade 1 or return to baseline. • **Resume** KRAZATI at the next lower dose level.
	AST or ALT > 3 x ULN with total bilirubin > 2 x ULN in the absence of alternative causes	• **Permanently discontinue** KRAZATI.
Interstitial Lung Disease/ Pneumonitis	Any Grade	• **Withhold** KRAZATI if ILD/ pneumonitis is suspected. • **Permanently discontinue** KRAZATI if ILD/ pneumonitis is confirmed.
Other Adverse Reactions	Grade 3 or 4	• **Withhold** KRAZATI until recovery to ≤ Grade 1 or return to baseline. • **Resume** KRAZATI at the next lower dose level.

*Grading defined by NCI CTCAE version 5.0.

ALT=alanine aminotransferase; AST=aspartate aminotransferase; ILD=interstitial lung disease; NCI CTCAE=National Cancer Institute Common Terminology Criteria for Adverse Events; ULN=upper limit of normal.

General Management of Diarrhea, Nausea, and Vomiting

Patients may experience GI ARs. In the pooled safety population, 89% of 366 patients experienced nausea, diarrhea, or vomiting.[1] Optimal management varies based on the symptoms. **Patients should be advised of the possibility of developing diarrhea, nausea, or vomiting. Refer to the FDA-approved patient labeling.**

DEFINITION OF SELECT GI ARs[4]

CTCAE Term	Grade 1	Grade 2	Grade 3	Grade 4
Diarrhea	Increase of <4 stools per day over baseline; mild increase in ostomy output compared to baseline	Increase of 4 - 6 stools per day over baseline; moderate increase in ostomy output compared to baseline; limiting instrumental ADL	Increase of ≥7 stools per day over baseline; hospitalization indicated; severe increase in ostomy output compared to baseline; limiting self care ADL	Life-threatening consequences; urgent intervention indicated
Nausea	Loss of appetite without alteration in eating habits	Oral intake decreased without significant weight loss, dehydration or malnutrition	Inadequate oral caloric or fluid intake; tube feeding, TPN, or hospitalization indicated	–
Vomiting	Intervention not indicated	Outpatient IV hydration; medical intervention indicated	Tube feeding, TPN, or hospitalization indicated	Life-threatening consequences

ADL=activities of daily living; CTCAE=Common Terminology Criteria for Adverse Events; GI=gastrointestinal; TPN=total parenteral nutrition.

Use of Common GI Concomitant Medications in KRYSTAL-1[5]

Nausea, diarrhea, and vomiting were manageable with dose reductions, interruptions, and/or use of supportive concomitant medications

- 48% of patients used antidiarrheals
- 87% of patients used antiemetics/antinauseants

There are no restrictions for use of PPIs in the KRAZATI Prescribing Information. No clinically significant differences in the PK of adagrasib were predicted or observed when used concomitantly with a PPI.[1]

53% of patients in the KRYSTAL-1 study were treated with PPIs

GI=gastrointestinal; PK=pharmacokinetics; PPI=proton pump inhibitor.

SELECT IMPORTANT SAFETY INFORMATION

Gastrointestinal Adverse Reactions

- KRAZATI can cause severe gastrointestinal adverse reactions
- Monitor and manage patients using supportive care, including antidiarrheals, antiemetics, or fluid replacement, as indicated. Withhold, reduce the dose, or permanently discontinue KRAZATI based on severity

Please see additional Important Safety Information on pages 24–25 and Full Prescribing Information.

KRAZATI® (adagrasib) | 200 mg TABLETS

General Management of Diarrhea, Nausea, and Vomiting

Advise patients that KRAZATI can cause severe GI ARs and to contact their healthcare provider for signs or symptoms of GI ARs.

NAUSEA/VOMITING

GENERAL ADVICE[6]

Advise patients to notify their healthcare provider if they experience vomiting over a period of days.

GENERAL MANAGEMENT TIPS[6]:

- Oral hydration
- Small, frequent meals
- Talk to your doctor about potentially using antiemetic

DIARRHEA

Patients should be advised to notify you at the first signs of loose stool or an increased frequency of bowel movements.[7]

GENERAL MANAGEMENT TIPS[7]:

- Oral hydration
- Small, frequent meals
- Avoidance of lactose-containing products, high-fat meals, and alcohol
- Talk to your doctor about potentially using an antidiarrheal

Monitor and manage patients using supportive care, including antidiarrheals, antiemetics, or fluid replacement, as indicated.

GI=gastrointestinal.

General Management of QTc Prolongation

GENERAL MANAGEMENT OF QTc PROLONGATION[1]

QTc interval prolongation may occur in patients treated with KRAZATI.

- KRAZATI can cause QTc interval prolongation, which can increase the risk for ventricular tachyarrhythmias (eg, torsades de pointes) or sudden death.
- In the pooled safety population, 6% of 366 patients with at least one post-baseline ECG assessment had an average QTc ≥501 ms and 11% of patients had an increase from baseline of QTc >60 msec. KRAZATI causes concentration-dependent increases in the QTc interval.
- Avoid concomitant use of KRAZATI with other products with a known potential to prolong the QTc interval. Avoid use of KRAZATI in patients with congenital long QT syndrome and in patients with concurrent QTc prolongation.
- Monitor ECGs and electrolytes prior to starting KRAZATI, during concomitant use, and as clinically indicated in patients with congestive heart failure, bradyarrhythmias, electrolyte abnormalities, and in patients who are unable to avoid concomitant medications that are known to prolong the QT interval. Withhold, reduce the dose, or permanently discontinue KRAZATI depending on severity.

DEFINITION OF QTc INTERVAL PROLONGATION[4]

	Grade 1	Grade 2	Grade 3	Grade 4
CTCAE Definition	Average QTc interval 450-480 msec	Average QTc interval 481-500 msec	Average QTc interval ≥501 msec; >60 msec change from baseline	Torsades de pointes; polymorphic ventricular tachycardia; signs/symptoms of serious arrhythmia

CTCAE=Common Terminology Criteria for Adverse Events; ECG=electrocardiogram.

Please see Important Safety Information on pages 24–25 and Full Prescribing Information.

Counseling Patients on Drug Interactions[1]

Be sure to get a complete list of other therapies your patients take, including prescription medicines, over-the-counter drugs, vitamins, and herbal products. Doing so can help you take action to address any potential interactions that could affect the safety of therapies, including KRAZATI.

Effects of Other Drugs on KRAZATI[1]

Concomitant Drug	KRAZATI Dosage	Changes in C_{max} or AUC of KRAZATI	
		C_{max} % Decrease	AUC % Decrease
Rifampin (a strong CYP3A inducer)	600 mg single dose	88%	95%
	600 mg multiple doses	>61%*	>66%*

*Predicted changes in C_{max} or AUC of KRAZATI.

AUC=area under the plasma concentration-time curve; C_{max}=maximum plasma concentration.

Effects of Other Drugs on KRAZATI[1]

STRONG CYP3A4 INDUCERS

Avoid concomitant use of KRAZATI with strong CYP3A inducers.

KRAZATI is a CYP3A4 substrate. Concomitant use of KRAZATI with a strong CYP3A inducer reduces KRAZATI exposure, which may reduce the effectiveness of KRAZATI.

STRONG CYP3A4 INHIBITORS

Avoid concomitant use of KRAZATI with strong CYP3A inhibitors until adagrasib concentrations have reached steady state (after approximately 8 days).

KRAZATI is a CYP3A4 substrate. If KRAZATI concentrations have not reached steady state, concomitant use of a strong CYP3A inhibitor will increase adagrasib concentrations, which may increase the risk of KRAZATI adverse reactions.

Effects of KRAZATI on Other Drugs[1]

Concomitant Drug	KRAZATI Dosage	Fold Increase of Concomitant Drug	
		C_{max}	AUC
Midazolam (a sensitive CYP3A substrate)	400 mg* twice daily	4.8-fold	21-fold
	600 mg twice daily	3.1-fold†	31-fold†
Warfarin (a sensitive CYP2C9 substrate)	600 mg twice daily	1.1-fold†	2.9-fold†
Dextromethorphan (a sensitive CYP2D6 substrate)	400 mg* twice daily	1.9-fold	1.8-fold
	600 mg twice daily	1.7-fold†	2.4-fold†
Digoxin (a P-gp substrate)	600 mg twice daily	1.9-fold†	1.5-fold†

*0.66 times the approved recommended dosage.
†Predicted changes in C_{max} or AUC of concomitant drug.

AUC=area under the plasma concentration-time curve; C_{max}=maximum plasma concentration.

Effects of KRAZATI on Other Drugs[1] (Cont'd)

SENSITIVE CYP3A SUBSTRATES

Avoid concomitant use of KRAZATI with sensitive CYP3A substrates unless otherwise recommended in the Prescribing Information for these substrates.

KRAZATI is a CYP3A inhibitor. Concomitant use with KRAZATI increases exposure of CYP3A substrates, which may increase the risk of adverse reactions related to these substrates.

SENSITIVE CYP2C9 OR CYP2D6 SUBSTRATES

Avoid concomitant use of KRAZATI with sensitive CYP2C9 or CYP2D6 substrates where minimal concentration changes may lead to serious adverse reactions unless otherwise recommended in the Prescribing Information for these substrates.

KRAZATI is an inhibitor to CYP2C9 and CYP2D6. Concomitant use of KRAZATI increases exposure of these substrates, which may increase the risk of adverse reactions related to these substrates.

P-gp SUBSTRATES

Avoid concomitant use of KRAZATI with P-gp substrates where minimal concentration changes may lead to serious adverse reactions unless otherwise recommended in the Prescribing Information for these substrates.

KRAZATI is a P-gp inhibitor. Concomitant use with KRAZATI increases exposure of P-gp substrates, which may increase the risk of adverse reactions related to these substrates.

Please see Important Safety Information on pages 24–25 and Full Prescribing Information.

PRODUCTS KNOWN TO PROLONG THE QTc

Avoid concomitant use of KRAZATI with other products with a known potential to prolong the QTc interval. If concomitant use cannot be avoided, monitor electrocardiogram and electrolytes prior to starting KRAZATI, during concomitant use, and as clinically indicated. Withhold KRAZATI if the QTc interval is >500 ms or the change from baseline is >60 ms.

KRAZATI causes QTc interval prolongation. Concomitant use of KRAZATI with other products that prolong the QTc interval may result in a greater increase in the QTc interval and adverse reactions associated with QTc interval prolongation, including Torsade de pointes, other serious arrhythmias, and sudden death.

Examples of medications/substances to avoid[5]*		
Azithromycin	Erythromycin	Loperamide†
Chlorpromazine	Escitalopram	Moxifloxacin
Ciprofloxacin	Fluconazole	Ondansetron†
Citalopram	Gatifloxacin	
Clarithromycin	Levofloxacin	

*This is not a comprehensive list.

†If the following medications cannot be avoided, please see the following recommendations:

Loperamide: Oral administration at 0.5-1 mg per dose, up to 3 mg daily in patients without underlying bradycardia, congestive heart failure, or congenital long QT syndrome.

Ondansetron: Oral administration at doses up to 4 mg every 6 hours, with a maximum total daily dose of 16 mg, in patients without underlying bradycardia, congestive heart failure, or congenital long QT syndrome.

SELECT IMPORTANT SAFETY INFORMATION

QTc Interval Prolongation

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- Avoid concomitant use of KRAZATI with other products with a known potential to prolong the QTc interval. Avoid use of KRAZATI in patients with congenital long QT syndrome and in patients with concurrent QTc prolongation
- Monitor ECGs and electrolytes, particularly potassium and magnesium, prior to starting KRAZATI, during concomitant use, and as clinically indicated in patients with congestive heart failure, bradyarrhythmias, electrolyte abnormalities, and in patients who are unable to avoid concomitant medications that are known to prolong the QT interval. Correct electrolyte abnormalities. Withhold, reduce the dose, or permanently discontinue KRAZATI, depending on severity

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Use in Specific Populations[1]

Pregnancy

- There are no available data on the use of KRAZATI in pregnant women
- In animal reproduction studies, oral administration of KRAZATI to pregnant rats and rabbits during the period of organogenesis did not cause adverse development effects or embryo-fetal lethality at exposures below the human exposure at the recommended dose of 600 mg twice daily
- Please refer to the Prescribing Information for full information

Lactation

- There are no data on the presence of KRAZATI or its metabolites in human milk, the effects of KRAZATI on the breastfed child, or on milk production
- Because of the potential for serious adverse reactions in breastfed children, advise lactating women not to breastfeed during treatment with KRAZATI and for at least 1 week after the final dose

Females and Males of Reproductive Potential

- Infertility: Based on findings from animal studies, KRAZATI may impair fertility in females and males of reproductive potential

Pediatric Use

- The safety and effectiveness of KRAZATI has not been established in pediatric patients

Geriatric Use

- Of 116 patients who received KRAZATI 600 mg BID in KRYSTAL-1, 49% (57 patients) were ≥65 years of age
- No overall differences in safety or effectiveness were observed between older and younger patients

BID=twice-daily.

Drug Interactions

Getting Patients Started

PATIENT WELCOME KIT

Patients starting on treatment with KRAZATI will receive a welcome kit that includes:

- Information about starting treatment with KRAZATI
- A drug information card
- A pill tracker
- Other support items

PRODUCT AVAILABILITY

KRAZATI is available through select specialty pharmacies and distributors.

Please see Important Safety Information on pages 24–25 and Full Prescribing Information.

INDICATION

KRAZATI, as a single-agent, is indicated for the treatment of adult patients with KRAS G12C-mutated locally advanced or metastatic non-small cell lung cancer (NSCLC) as determined by an FDA-approved test, who have received at least one prior systemic therapy.

This indication is approved under accelerated approval based on objective response rate (ORR) and duration of response (DOR). Continued approval for this indication may be contingent upon verification and description of a clinical benefit in a confirmatory trial.

IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

Gastrointestinal Adverse Reactions

- KRAZATI can cause severe gastrointestinal adverse reactions
- Monitor and manage patients using supportive care, including antidiarrheals, antiemetics, or fluid replacement, as indicated. Withhold, reduce the dose, or permanently discontinue KRAZATI based on severity

QTc Interval Prolongation

- KRAZATI can cause QTc interval prolongation, which can increase the risk for ventricular tachyarrhythmias (eg, torsades de pointes) or sudden death
- Avoid concomitant use of KRAZATI with other products with a known potential to prolong the QTc interval. Avoid use of KRAZATI in patients with congenital long QT syndrome and in patients with concurrent QTc prolongation
- Monitor ECGs and electrolytes, particularly potassium and magnesium, prior to starting KRAZATI, during concomitant use, and as clinically indicated in patients with congestive heart failure, bradyarrhythmias, electrolyte abnormalities, and in patients who are unable to avoid concomitant medications that are known to prolong the QT interval. Correct electrolyte abnormalities. Withhold, reduce the dose, or permanently discontinue KRAZATI, depending on severity

Hepatotoxicity

- KRAZATI can cause hepatotoxicity, which may lead to drug-induced liver injury and hepatitis
- Monitor liver laboratory tests (AST, ALT, alkaline phosphatase, and total bilirubin) prior to the start of KRAZATI, and monthly for 3 months or as clinically indicated, with more frequent testing in patients who develop transaminase elevations. Reduce the dose, withhold, or permanently discontinue KRAZATI based on severity

KRAZATI® (adagrasib) 200 mg TABLETS

Click here to learn more about KRAZATI

IMPORTANT SAFETY INFORMATION (CONTINUED)

WARNINGS AND PRECAUTIONS (CONTINUED)

Interstitial Lung Disease/Pneumonitis

- KRAZATI can cause interstitial lung disease (ILD)/pneumonitis, which can be fatal
- Monitor patients for new or worsening respiratory symptoms indicative of ILD/pneumonitis (eg, dyspnea, cough, fever) during treatment with KRAZATI. Withhold KRAZATI in patients with suspected ILD/pneumonitis and permanently discontinue KRAZATI if no other potential causes of ILD/pneumonitis are identified

ADVERSE REACTIONS

- Serious adverse reactions occurred in 57% of 116 patients who received adagrasib in NSCLC patients. The most common adverse reactions in NSCLC patients (≥20%) were diarrhea, nausea, fatigue, vomiting, musculoskeletal pain, hepatotoxicity, renal impairment, dyspnea, edema, decreased appetite, cough, pneumonia, dizziness, constipation, abdominal pain, and QTc interval prolongation

DRUG INTERACTIONS

- Strong CYP3A4 Inducers: Avoid concomitant use.
- Strong CYP3A4 Inhibitors: Avoid concomitant use until adagrasib concentrations have reached steady state (after ~8 days).
- Sensitive CYP3A4 Substrates: Avoid concomitant use with sensitive CYP3A4 substrates.
- Sensitive CYP2C9 or CYP2D6 Substrates or P-gp Substrates: Avoid concomitant use with sensitive CYP2C9 or CYP2D6 substrates or P-gp substrates where minimal concentration changes may lead to serious adverse reactions.
- Drugs That Prolong QT Interval: Avoid concomitant use with KRAZATI.

Please see Drug Interactions Section of the Full Prescribing Information for additional information.

USE IN SPECIFIC POPULATIONS

Females and Males of Reproductive Potential

- Infertility: Based on findings from animal studies, KRAZATI may impair fertility in females and males of reproductive potential

Lactation

Advise not to breastfeed

Please see Full Prescribing Information.

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