FOR *KRAS G12C*-MUTATED ADVANCED CRC

INDICATION

KRAZATI in combination with cetuximab is indicated for the treatment of adult patients with KRAS G12C-mutated locally advanced or metastatic colorectal cancer (CRC), as determined by an FDA-approved test, who have received prior treatment with fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy.

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.

KRAZATI THERAPY MANAGEMENT GUIDE

for *KRAS G12C*-mutated advanced CRC

» Adagrasib (KRAZATI) is an NCCN Category 2A recommendation in the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®): colon and rectal cancers[1,2]

NCCN=National Comprehensive Cancer Network.

SELECT IMPORTANT SAFETY INFORMATION

The KRAZATI Full Prescribing Information contains Warnings and Precautions for Gastrointestinal Adverse Reactions, QTc Interval Prolongation, Hepatotoxicity, and Interstitial Lung Disease/Pneumonitis.

Please see Important Safety Information on pages 20-22 and Full Prescribing Information.

KRAZATI® (adagrasib) 200 mg TABLETS

KRAZATI® (adagrasib) | 200 mg TABLETS

KRAZATI in combination with cetuximab is indicated for the treatment of adult patients with *KRAS G12C*-mutated locally advanced or metastatic colorectal cancer (CRC), as determined by an FDA-approved test, who have received prior treatment with fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy.

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' KRAZATI therapy throughout their treatment journey.

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

Please see the Full Prescribing Information for more information.

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 Important Safety Information on pages 20-22 and Full Prescribing Information.

TABLE OF CONTENTS

Dosing 4

Adverse Reactions (ARs) 5

Monitoring Your Patients 7

Dosage Modifications 8

Management of ARs 10

Drug Interactions 14

- Counseling patients on drug interactions 14
- Effects of other drugs on KRAZATI 14
- Effects of KRAZATI on other drugs 15

Use in Specific Populations 18

Patient Support 19

Important Safety Information 20

KRAZATI + cetuximab infusion therapy

KRAZATI recommended dosage: 600 mg BID[3]

Until disease progression or unacceptable toxicity

AM FIRST DOSE
Take (3) 200-mg tablets by mouth in the morning

PM SECOND DOSE
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

KRAZATI is 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** of KRAZATI by more than 4 hours or if vomiting occurs after taking KRAZATI, advise patient not to take an additional dose. 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

Treatment with KRAZATI as a **single agent** may be continued if cetuximab is permanently discontinued.

For combination treatment, withhold or permanently discontinue cetuximab when KRAZATI is withheld or permanently discontinued.

Refer to the cetuximab Prescribing Information for cetuximab dosage information

BID=twice-daily; PPI=proton pump inhibitor.

Please see Important Safety Information on pages 20-22 and Full Prescribing Information.

Adverse reactions (ARs) with KRAZATI + cetuximab[3]

The safety of KRAZATI combined with cetuximab was evaluated in patients with *KRAS G12C*-mutated, locally advanced or metastatic CRC. Patients initiated treatment with KRAZATI 600 mg BID in combination with cetuximab weekly (n=17) or every 2 weeks (n=77). Among patients who received KRAZATI + cetuximab, 60% were exposed for greater than 6 months and 12% were exposed for greater than 12 months.

ARs (≥20%) IN PATIENTS WITH *KRAS G12C*-MUTATED CRC WHO RECEIVED KRAZATI IN COMBINATION WITH CETUXIMAB IN KRYSTAL-1[3,4]

Adverse Reaction*	KRAZATI in Combination With Cetuximab (N=94)				
	Grade 1 (%)	Grade 2 (%)	Grade 3 (%)	Grade 4 (%)	All Grades (%)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS					
Rash†	51.1	28.7	4.3	0	84
Dry skin	26.6	9.6	0	0	36.2
GASTROINTESTINAL DISORDERS					
Nausea	41.5	24.5	2.1	0	68.1
Diarrhea†	41.5	18.1	5.3	0	64.9
Vomiting†	36.2	21.3	0	0	57.4
Abdominal Pain†	13.8	11.7	4.3	0	29.8
Constipation	18.1	5.3	0	0	23.4
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS					
Fatigue†	25.5	28.7	3.2	0	57.4
Musculoskeletal pain†	28.7	13.8	4.3	0	46.8
Edema†	17	10.6	0	0	27.7
HEPATOBILIARY DISORDERS					
Hepatotoxicity†	19.1	9.6	8.5	1.1	38.3
NERVOUS SYSTEM DISORDERS					
Headache	21.3	11.7	4.3	0	37.2
Dizziness†	17	5.3	2.1	0	24.5
Peripheral neuropathy†	12.8	6.4	1.1	0	20.2
METABOLISM AND NUTRITION DISORDERS					
Decreased appetite	13.8	16	0	0	29.8
BLOOD AND LYMPHATIC SYSTEM DISORDERS					
Anemia	11.7	7.4	7.4	0	26.6
RESPIRATORY					
Cough†	14.9	9.6	0	0	24.5

*Graded per CTCAE version 5.0.
†Grouped term; includes multiple related terms.

BID=twice-daily; CRC=colorectal cancer; CTCAE=Common Terminology Criteria for Adverse Events.

Please see Important Safety Information on pages 20-22 and Full Prescribing Information.

SELECTED LABORATORY ABNORMALITIES (≥25%) IN PATIENTS WHO RECEIVED KRAZATI IN COMBINATION WITH CETUXIMAB IN KRYSTAL-1

Laboratory Abnormality	KRAZATI in Combination With Cetuximab*	
	All Grades (%)	Grade 3 or 4 (%)
Hematology		
Lymphocytes decreased	63	17
Hemoglobin decreased	48	5
Leukocytes decreased	27	1.1
Chemistry		
Alanine aminotransferase increased	51	2.2
Magnesium decreased	49	7
Albumin decreased	46	2.2
Lipase increased	41	3.3
Potassium decreased	40	9
Aspartate aminotransferase increased	39	4.3
Creatinine increased	30	1.1
Sodium decreased	30	0
Calcium decreased	29	1.1
Amylase increased	29	0
Alkaline phosphate increased	29	1.1

*Denominator used to calculate the rate varied from 82 to 92 based on the number of patients with a baseline value and at least one post-treatment value.

CRC=colorectal cancer.

Please see Important Safety Information on pages 20-22 and Full Prescribing Information.

Monitoring your patients[3]

Monitoring and support for your patients is important at the start of and throughout treatment. 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, 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
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

Withhold, reduce the dose, or permanently discontinue KRAZATI depending on severity (see Dosage and Administration in Full Prescribing Information).

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

Please see Important Safety Information on pages 20-22 and Full Prescribing Information.

KRAZATI dosage modifications for adverse reactions[3]

RECOMMENDED DOSAGE	FIRST DOSE REDUCTION	SECOND DOSE REDUCTION
600 mg BID	**400 mg BID**	**600 mg QD**
(3) 200-mg tablets	(2) 200-mg tablets	(3) 200-mg tablets

If ARs occur, a maximum of 2 dose reductions are permitted. Permanently discontinue KRAZATI in patients who are unable to tolerate 600 mg once daily.

Dosage modifications in KRYSTAL-1 (phase 1/2) N=94

Dosage interruptions due to an adverse reaction (AR) occurred in 62% of patients

- ARs requiring dosage interruption in ≥2.0% of patients who received KRAZATI included diarrhea, nausea, vomiting, abdominal pain, dizziness, headache, pneumonia, alanine aminotransferase increased, aspartate aminotransferase increased, dyspnea, fatigue, pleural effusion, rash, anemia, electrocardiogram QT prolongation, blood bilirubin increased, blood creatinine increased, decreased appetite, dehydration, hemorrhage, hypomagnesemia, lipase increased, muscular weakness, musculoskeletal pain, and pyrexia

Dosage reductions due to an AR occurred in 35% of patients

- ARs requiring dose reductions in ≥2.0% of patients who received KRAZATI included fatigue, increased aspartate aminotransferase, increased alanine aminotransferase, nausea, decreased appetite, electrocardiogram QT prolongation, dizziness, acute kidney injury, diarrhea, dysarthria, and vomiting

2% of patients discontinued due to an AR[3,5]

- Permanent discontinuation of KRAZATI due to an AR occurred in 2 patients due to abdominal pain and prolonged QT interval (1 patient each). TRAEs led to the discontinuation of cetuximab in 8 patients (8.5%)

Serious ARs were reported in 30% of patients who received KRAZATI in combination with cetuximab. The most common serious ARs (≥2%) were pneumonia (4.3%), pleural effusion, pyrexia, acute kidney injury, dehydration, and small intestinal obstruction (2.1% each). A fatal AR of pneumonia occurred in 1 patient who received KRAZATI in combination with cetuximab.

If you determine that a dosage reduction is necessary, your patient can continue KRAZATI therapy at the next lower dose without immediately requiring a new prescription

See dosage modifications for certain ARs on page 9.

BID=twice-daily; QD=once-daily; TRAE=treatment-related adverse event.

Please see Important Safety Information on pages 20-22 and Full Prescribing Information.

Dosage modifications for adverse reactions (ARs)[3]

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) *See page 12 for definitions.*	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 *See page 14 for definitions.*	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 *See page 15 for definitions.*	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.

†When KRAZATI is administered in combination with cetuximab, withhold or permanently discontinue treatment with cetuximab when withholding or permanently discontinuing treatment with KRAZATI.

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

Please see Important Safety Information on pages 20-22 and Full Prescribing Information.

General management of diarrhea, nausea, and vomiting[3]

Patients may experience GI ARs. In patients who received KRAZATI + cetuximab, 92% of 94 patients, including 6% Grade 3, experienced nausea, diarrhea, or vomiting. 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[6]

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; IV=intravenous; TPN=total parenteral nutrition.

Please see Important Safety Information on pages 20-22 and Full Prescribing Information.

General management of diarrhea, nausea, and vomiting[3] *(Continued)*

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[7]

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

General management tips[7]:

- Oral hydration
- Small, frequent meals
- Consider administering an antiemetic as you deem appropriate

DIARRHEA

Patients should be advised to notify you at the first signs of loose stool or an increased frequency of bowel movements.[8]

General management tips[8]:

- Oral hydration
- Small, frequent meals
- Avoidance of lactose-containing products, high-fat meals, and alcohol
- Consider administering an antidiarrheal as you deem appropriate

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

Withhold, reduce the dose, or permanently discontinue KRAZATI depending on severity (see Dosage and Administration in Full Prescribing Information).

GI=gastrointestinal.

General management of QTc prolongation[3]

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 patients who received KRAZATI in combination with cetuximab, 5% of 93 patients with at least one post-baseline electrocardiogram (ECG) assessment had an average QTc ≥501 msec and 16% of patients had an increase from baseline of QTc >60 msec
- 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

DEFINITION OF QTc INTERVAL PROLONGATION[6]

	Grade 1	Grade 2	Grade 3	Grade 4
CTCAE Definition	Average QTc interval 450-480 ms	Average QTc interval 481-500 ms	Average QTc interval ≥501 ms; >60 ms 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 20-22 and Full Prescribing Information.

General management of hepatotoxicity[3]

KRAZATI can cause hepatotoxicity, which may lead to drug-induced liver injury and hepatitis.

In patients who received KRAZATI in combination with cetuximab, 29% had increased alanine aminotransferase (ALT)/increased aspartate aminotransferase (AST); 5% were Grade 3 and 1.1% were Grade 4. The median time to first onset of increased 8 ALT/AST was 4 weeks (range: 0.1 to 27). Overall hepatotoxicity occurred in 38%, and 10% were Grade 3 or 4. Hepatotoxicity leading to KRAZATI dose interruption or reduction occurred in 12% of patients.

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.

DEFINITION OF HEPATOXICITY[6]

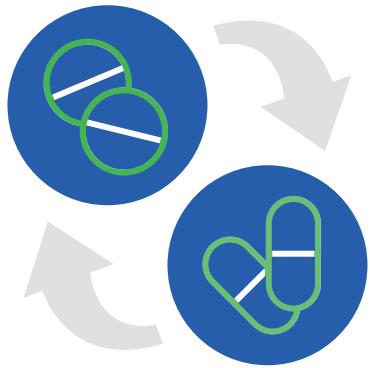
	ALT Increased or AST Increased	Grade 1	Grade 2	Grade 3	Grade 4
CTCAE Definition	**If baseline was normal**	>ULN-3.0 x ULN	>3.0-5.0 x ULN	>5.0-20.0 x ULN	>20.0 x ULN
	If baseline was abnormal	1.5-3.0 x baseline	>3.0-5.0 x baseline	>5.0-20.0 x baseline	>20.0 x baseline

ALT=alanine aminotransferase; AST=aspartate aminotransferase; ULN=upper limit of normal.

Please see Important Safety Information on pages 20-22 and Full Prescribing Information.

Counseling patients on drug interactions[3]

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[3]

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.

Please see Important Safety Information on pages 20-22 and Full Prescribing Information.

Effects of other drugs on KRAZATI[3] *(Continued)*

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 KRAZATI 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 KRAZATI concentrations, which may increase the risk of KRAZATI adverse reactions.

Effects of KRAZATI on other drugs[3]

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.

Please see Important Safety Information on pages 20-22 and Full Prescribing Information.

Effects of KRAZATI on other drugs[3] *(Continued)*

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.

SELECT IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

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 Important Safety Information on pages 20-22 and Full Prescribing Information.

Effects of KRAZATI on other drugs[3] *(Continued)*

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.

PRODUCTS KNOWN TO PROLONG THE QTc INTERVAL

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[9]*		
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.

Please see Important Safety Information on pages 20-22 and Full Prescribing Information.

Use in specific populations[3]

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
- Of 99 patients who received adagrasib 600 mg orally twice daily in combination with cetuximab, 33% (33 patients) were ≥65 years of age
- No overall differences in safety or effectiveness were observed between older and younger patients

BID=twice-daily.

Please see Important Safety Information on pages 20-22 and Full Prescribing Information.

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.

REFERENCES: 1. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Colon Cancer V.3.2024. © National Comprehensive Cancer Network, Inc. 2024. All rights reserved. Accessed June 11, 2024. To view the most recent and complete version of the guideline, go online to NCCN.org. NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way. **2.** Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Rectal Cancer V.2.2024. © National Comprehensive Cancer Network, Inc. 2024. All rights reserved. Accessed June 11, 2024. To view the most recent and complete version of the guideline, go online to NCCN.org. **3.** KRAZATI®. Prescribing information. Princeton, NJ. Mirati Therapeutics, Inc., a Bristol Myers Squibb company; 2024. **4.** Data on file. BMS-REF-ADAG-0021. Princeton, NJ: Mirati Therapeutics, Inc., a Bristol Myers Squibb company; 2024. **5.** Yaeger R, Uboha NV, Pelster MS, et al. Efficacy and safety of adagrasib plus cetuximab in patients with *KRAS*^{G12C}-mutated metastatic colorectal cancer. *Cancer Discov*. Published online April 8, 2024. doi:10.1158/2159-8290.CD-24-0217 **6.** Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. U.S. Department of Health And Human Services. November 27, 2017. Accessed February 23, 2022. https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/ CTCAE_v5_Quick_ Reference_5x7.pdf **7.** Managing nausea and vomiting at home. American Cancer Society. Updated September 10, 2020. Accessed July 13, 2022. https://www.cancer.org/treatment/treatments-and-side-effects/physical-side-effects/ nausea-and-vomiting/managing.html **8.** Diarrhea. American Cancer Society. Updated February 1, 2020. Accessed July 13, 2022. https://www.cancer.org/treatment/treatments-and-side-effects/physical-side-effects/stool or-urine-changes/diarrhea.html **9.** Zhang J, Johnson M, Barve M, et al. Practical guidance for the management of adverse events in patients with KRASG12C-mutated non-small cell lung cancer receiving adagrasib. *Oncologist.* 2023;28(4):287-296.

INDICATION AND IMPORTANT SAFETY INFORMATION

INDICATION

KRAZATI in combination with cetuximab is indicated for the treatment of adult patients with KRAS G12C-mutated locally advanced or metastatic colorectal cancer (CRC), as determined by an FDA-approved test, who have received prior treatment with fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy.

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

Please see additional Important Safety Information on pages 21-22 and Full Prescribing Information.

IMPORTANT SAFETY INFORMATION *(Continued)*

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

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 30% of 94 patients who received adagrasib in combination with cetuximab. The most common adverse reactions in CRC patients (≥20%) were rash, nausea, diarrhea, vomiting, fatigue, musculoskeletal pain, hepatotoxicity, headache, dry skin, abdominal pain, decreased appetite, edema, anemia, dizziness, cough, constipation, and peripheral neuropathy

Please see additional Important Safety Information on page 22 and Full Prescribing Information.

IMPORTANT SAFETY INFORMATION *(Continued)*

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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