TUKYSA®
tucatinib
50 mg | 150 mg tablets

TUKYSA + trastuzumab

DOSING AND ADMINISTRATION GUIDE

This guide provides an overview of appropriate dosing and administration of TUKYSA

- Getting started with TUKYSA
- Managing drug interactions
- Monitoring for adverse reactions
- Accessing patient support resources
- Modifying dosing

Indication

TUKYSA is indicated in combination with trastuzumab for the treatment of adult patients with *RAS* wild-type, HER2-positive unresectable or metastatic colorectal cancer that has progressed following treatment with fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy.

This indication is approved under accelerated approval based on tumor response rate and durability of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.

Select Important Safety Information

The labeling for TUKYSA contains warnings and precautions for diarrhea, hepatotoxicity, and embryo-fetal toxicity, some of which may be severe or fatal.

- If diarrhea occurs, administer antidiarrheal treatment as clinically indicated. Based on the severity of the diarrhea, interrupt dose, then dose reduce or permanently discontinue TUKYSA.
- Monitor ALT, AST, and bilirubin prior to starting TUKYSA, every 3 weeks during treatment, and as clinically indicated. Based on the severity of hepatotoxicity, interrupt dose, then dose reduce or permanently discontinue TUKYSA.
- Advise females of reproductive potential, and male patients with female partners of reproductive potential, of the potential risk to a fetus and to use effective contraception. See full Prescribing Information for further management instructions.

The most common serious adverse reactions in ≥2% of patients who received TUKYSA in combination with trastuzumab were intestinal obstruction, urinary tract infection, pneumonia, abdominal pain, and rectal perforation.

The most common adverse reactions in ≥20% of patients who received TUKYSA in combination with trastuzumab were diarrhea, fatigue, rash, nausea, abdominal pain, infusion-related reactions, and pyrexia.

ALT = alanine aminotransferase; AST = aspartate aminotransferase; HER = human epidermal growth factor receptor; mCRC = metastatic colorectal cancer; *RAS* = rat sarcoma virus.

Please see Important Safety Information and the accompanying full Prescribing Information.

Important Safety Information

Warnings and Precautions

- **Diarrhea:** TUKYSA can cause severe diarrhea including dehydration, hypotension, acute kidney injury, and death. If diarrhea occurs, administer antidiarrheal treatment as clinically indicated. Perform diagnostic tests as clinically indicated to exclude other causes of diarrhea. Based on the severity of the diarrhea, interrupt dose, then dose reduce or permanently discontinue TUKYSA.

  In MOUNTAINEER, when TUKYSA was given in combination with trastuzumab, diarrhea occurred in 64% of patients, including Grade 3 (3.5%), Grade 2 (10%), and Grade 1 (50%).
- **Hepatotoxicity:** TUKYSA can cause severe hepatotoxicity. Monitor ALT, AST, and bilirubin prior to starting TUKYSA, every 3 weeks during treatment, and as clinically indicated. Based on the severity of hepatotoxicity, interrupt dose, then dose reduce or permanently discontinue TUKYSA.

  In MOUNTAINEER, 6% of patients had a bilirubin increase > 3 × ULN (Grade ≥3), 6% had an AST increase > 5 × ULN, and 4.7% had an ALT increase > 5 × ULN. Hepatotoxicity led to dose reduction of TUKYSA in 3.5% of patients and discontinuation of TUKYSA in 2.3% of patients.
- **Embryo-Fetal Toxicity:** TUKYSA can cause fetal harm. Advise pregnant women and females of reproductive potential of the potential risk to a fetus. Advise females of reproductive potential, and male patients with female partners of reproductive potential, to use effective contraception during TUKYSA treatment and for 1 week after the last dose.

Adverse Reactions

Serious adverse reactions occurred in 22% of patients; the most common (in ≥2% of patients) were intestinal obstruction (7%), urinary tract infection (3.5%), pneumonia, abdominal pain, and rectal perforation (2.3% each).

Adverse reactions leading to permanent discontinuation of TUKYSA occurred in 6% of patients; the most common (in ≥2% of patients) was increased ALT (2.3%). Adverse reactions leading to dosage interruption occurred in 23% of patients; the most common (in ≥3% of patients) were increased ALT and diarrhea (3.5% each). Adverse reactions leading to dose reduction occurred in 9% of patients; the most common (in ≥2% of patients) were increased ALT and diarrhea (2.3% each).

The most common adverse reactions (≥20%) in patients treated with TUKYSA and trastuzumab were diarrhea, fatigue, rash, nausea, abdominal pain, infusion-related reactions, and pyrexia.

Other adverse reactions (<10%) include epistaxis (7%), weight decreased (7%), oropharyngeal pain (5%), oral dysesthesia (1%), and stomatitis (1%).

Lab Abnormalities

In MOUNTAINEER, Grade ≥3 laboratory abnormalities reported in ≥5% of patients who received TUKYSA were decreased lymphocytes, decreased sodium, increased AST, and increased bilirubin.

The mean increase in serum creatinine was 32% within the first 21 days of treatment with TUKYSA. The serum creatinine increases persisted throughout treatment and were reversible in 87% of patients with values outside normal lab limits upon treatment completion. Consider alternative markers of renal function if persistent elevations in serum creatinine are observed.

Drug Interactions

- **Strong CYP3A/Moderate CYP2C8 Inducers:** Concomitant use may decrease TUKYSA activity. Avoid concomitant use of TUKYSA.
- **Strong or Moderate CYP2C8 Inhibitors:** Concomitant use of TUKYSA with a strong CYP2C8 inhibitor may increase the risk of TUKYSA toxicity; avoid concomitant use. Increase monitoring for TUKYSA toxicity with moderate CYP2C8 inhibitors.
- **CYP3A Substrates:** Concomitant use may increase the toxicity associated with a CYP3A substrate. Avoid concomitant use of TUKYSA with a CYP3A substrate, where minimal concentration changes may lead to serious or life-threatening toxicities. If concomitant use is unavoidable, decrease the CYP3A substrate dosage.
- **P-gp Substrates:** Concomitant use may increase the toxicity associated with a P-gp substrate. Consider reducing the dosage of P-gp substrates, where minimal concentration changes may lead to serious or life-threatening toxicities.

Use in Specific Populations

- **Lactation:** Advise women not to breastfeed while taking TUKYSA and for 1 week after the last dose.
- **Hepatic Impairment:** Reduce the dose of TUKYSA for patients with severe (Child-Pugh C) hepatic impairment.

REF-7647_FINAL_01/23

Please see the accompanying full Prescribing Information.

TUKYSA® tucatinib
50 mg | 150 mg tablets

Getting started with TUKYSA[1]

TUKYSA is an oral medication taken twice a day, every day, in combination with trastuzumab

- Select patients for treatment of unresectable or metastatic colorectal cancer with TUKYSA based on the presence of HER2 overexpression or gene amplification and *RAS* WT
- An FDA-approved test for the detection of HER2 overexpression and gene amplification in patients with unresectable or metastatic colorectal cancer is not currently available

Dosing of TUKYSA should continue until disease progression or unacceptable toxicity

TUKYSA 300 mg orally, twice daily, ~12 hours apart at the same time each day, taken **with or without a meal**	**Continuously**
Trastuzumab* Intravenous dosing: initial dose 8 mg/kg, subsequent doses 6 mg/kg	Every 21 days

*Refer to full Prescribing Information for trastuzumab for dose modifications.

- TUKYSA may be dispensed in a 30-day supply and should be taken continuously

Monitor ALT, AST, and bilirubin prior to starting TUKYSA, every 3 weeks during treatment, and as clinically indicated.

Additional dosing and administration information

- For patients with severe hepatic impairment (Child-Pugh C), the recommended starting dose is 200 mg orally, twice daily
- Avoid concomitant use of strong CYP2C8 inhibitors with TUKYSA. If concomitant use with a strong CYP2C8 inhibitor cannot be avoided, reduce the recommended dosage to 100 mg orally, twice daily. After discontinuation of the strong CYP2C8 inhibitor for 3 elimination half-lives, resume the TUKYSA dose that was taken prior to initiating the inhibitor
- TUKYSA tablets should be swallowed whole; they should not be chewed, crushed, or split prior to swallowing
- If the patient vomits or misses a dose of TUKYSA, the next dose should be taken at the regularly scheduled time
- Please refer to the full Prescribing Information to learn how to modify the dose for select adverse reactions associated with TUKYSA
- For a list of drug-drug interactions, please see **Important Safety Information**

Learn more about dose modifications for adverse reactions on page 7.

CYP = cytochrome P450; FDA = US Food and Drug Administration; WT = wild type.

Please see additional Important Safety Information and the accompanying full Prescribing Information.

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Getting started with TUKYSA[1] (cont'd)

Dosage form and strengths		How supplied
  **50 mg***	Round, yellow, film-coated, debossed with "TUC" on one side and "50" on the other side	60 count in 75 cc bottle: NDC 51144-001-60
  **150 mg***	Oval-shaped, yellow, film-coated, debossed with "TUC" on one side and "150" on the other side	60 count in 75 cc bottle: NDC 51144-002-60 120 count in 150 cc bottle: NDC 51144-002-12

*Images are not to scale.

Storage

- Store at controlled room temperature, 20°C to 25°C (68°F to 77°F); excursions permitted from 15°C to 30°C (59°F to 86°F)

Special handling

- Dispense to patient in original container only. Store in original container to protect from moisture. Replace cap securely each time after opening. Do not discard desiccant
- Once opened, the product must be used within 3 months. Discard any unused tablets 3 months after opening the bottle

Please see additional Important Safety Information and the accompanying full Prescribing Information.

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Adverse reactions in MOUNTAINEER

Of the most common adverse reactions, a majority were Grade 1 or 2[1]

Adverse reactions in ≥10% of patients[1]		
	TUKYSA + trastuzumab (N = 86*)	
	All grades (%)	Grade 3 (%)
Gastrointestinal disorders		
Diarrhea	64	3.5
Nausea	35	0
Vomiting	16	0
Abdominal pain†	21	2.3
Constipation	14	1.2
General disorders		
Fatigue	44	2.3
Pyrexia	20	0
Chills	19	1.2
Skin and subcutaneous disorders		
Rash‡	37	0
Injury, poisoning, and procedural complications		
Infusion-related reaction	21	0
Metabolism and nutrition disorders		
Decreased appetite	19	0
Blood and lymphatic system disorders		
Anemia	10	0
Vascular disorders		
Hypertension	17	7
Musculoskeletal and connective tissue disorders		
Back pain	17	2.3
Arthralgia	16	1.2
Myalgia	13	0
Respiratory, thoracic, and mediastinal disorders		
Cough	16	0
Dyspnea	14	0
Psychiatric disorders		
Anxiety	10	0

- No Grade 5 adverse reactions were reported in the trial[2]
- Serious adverse reactions occurred in 22% of patients[1]
- Serious adverse reactions that occurred in ≥2% of patients were intestinal obstruction (7%), urinary tract infection (3.5%), pneumonia (2.3%), abdominal pain (2.3%), and rectal perforation (2.3%)[1]
- Laboratory abnormalities of any grade occurring in ≥15% of patients treated with TUKYSA + trastuzumab in MOUNTAINEER[1]:
  - Hematology: decreased hemoglobin (46% [Grade ≥3, 3.5%]), decreased lymphocytes (39%), decreased leukocytes (22%), and decreased platelets (15%)
  - Chemistry: increased creatinine (58%),§ increased glucose (56%), increased ALT (46%), increased AST (33%), increased bilirubin (28%), increased alkaline phosphatase (25%), decreased albumin (24%), decreased sodium (20%), and decreased potassium (16%)

*Includes 1 patient who only received trastuzumab.[1]
†Abdominal pain includes abdominal discomfort, abdominal pain, and abdominal pain upper.[1]
‡Rash includes acne, dermatitis acneiform, dermatitis contact, erythema, erythema multiforme, rash, rash macular, rash maculo-papular, rash papular, rash pustular, skin exfoliation, and urticaria.[1]
§Due to inhibition of renal tubular transport of creatinine without affecting glomerular function.[1]

Please see additional Important Safety Information and the accompanying full Prescribing Information.

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Monitoring for adverse reactions[1]

The Prescribing Information for TUKYSA contains warnings and precautions for diarrhea, hepatotoxicity, and embryo-fetal toxicity, some of which may be severe or fatal. Please see full Important Safety Information for more details.

Diarrhea

- TUKYSA can cause severe diarrhea including dehydration, hypotension, acute kidney injury, and death
  - 64% of patients experienced diarrhea, with 3.5% experiencing a Grade 3 event
- Diarrhea led to dose interruption in 3.5% of patients and dose reduction in 2.3% of patients
- If diarrhea occurs, administer antidiarrheal treatment and perform diagnostic tests to exclude other causes, as clinically indicated. Based on the severity, interrupt dose and then dose reduce or permanently discontinue TUKYSA

Hepatotoxicity

- TUKYSA can cause severe hepatotoxicity
  - 6% of patients had a bilirubin increase >3 × ULN (Grade ≥3), 6% had an AST increase >5 × ULN, and 4.7% had an ALT increase >5 × ULN
- Hepatotoxicity led to dose reduction of TUKYSA in 3.5% of patients and permanent discontinuation of TUKYSA in 2.3% of patients
- Monitor ALT, AST, and bilirubin prior to starting TUKYSA, every 3 weeks during treatment, and as clinically indicated. Based on the severity of hepatotoxicity, interrupt dose, then dose reduce or permanently discontinue TUKYSA

Monitor ALT, AST, and bilirubin prior to starting TUKYSA, every 3 weeks during treatment, and as clinically indicated

See page 7 for dose modifications to manage diarrhea and hepatotoxicity.

Dose interruptions, reductions, and permanent discontinuations due to adverse reactions

	TUKYSA + trastuzumab (N = 86)
Permanent discontinuation	6%
Reduction	9%
Interruption	23%

- The adverse reaction which resulted in permanent discontinuation of TUKYSA in ≥2% of patients was increased ALT (2.3%)
- Adverse reactions which required dose reductions in ≥2% of patients were increased ALT (2.3%) and diarrhea (2.3%)
- Adverse reactions which required dose interruption in ≥3% of patients were increased ALT (3.5%) and diarrhea (3.5%)

ULN = upper limit of normal.

Please see additional Important Safety Information and the accompanying full Prescribing Information.

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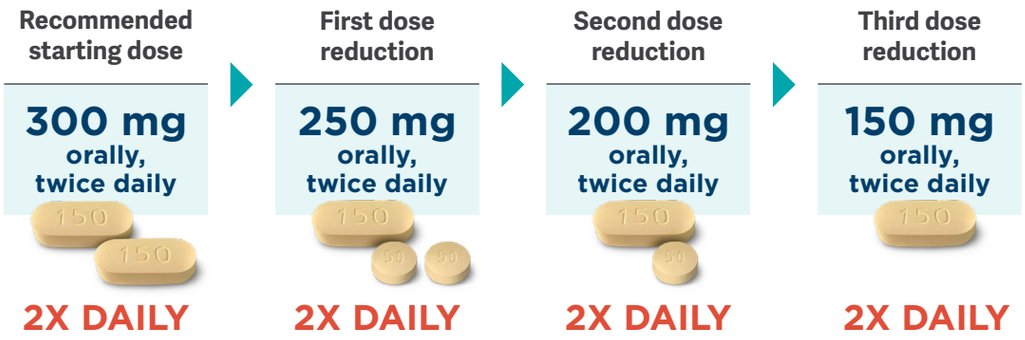
Modifying the TUKYSA dose[1]

Reduce TUKYSA in increments of 50 mg to manage adverse reactions



- Some patients may require dose modifications or permanent discontinuations of therapy to manage adverse reactions
- In MOUNTAINEER, 9% of patients had their TUKYSA dose reduced and 6% permanently discontinued TUKYSA due to adverse reactions
- Permanently discontinue TUKYSA in patients unable to tolerate 150 mg orally, twice daily

Trastuzumab dosing may be modified in accordance with its Prescribing Information.

Recommended TUKYSA dose modifications for adverse reactions

Adverse reaction	Severity	TUKYSA dose modification
Diarrhea	Grade 3 without anti-diarrheal treatment	Initiate or intensify appropriate medical therapy. Hold TUKYSA until recovery to ≤ Grade 1, then resume TUKYSA at the same dose level.
	Grade 3 with anti-diarrheal treatment	Initiate or intensify appropriate medical therapy. Hold TUKYSA until recovery to ≤ Grade 1, then resume TUKYSA at the next lower dose level.
	Grade 4	Permanently discontinue TUKYSA.
Hepatotoxicity	Grade 2 bilirubin (>1.5 to 3 × ULN)	Hold TUKYSA until recovery to ≤ Grade 1, then resume TUKYSA at the same dose level.
	Grade 3 ALT or AST (>5 to 20 × ULN) OR Grade 3 bilirubin (>3 to 10 × ULN)	Hold TUKYSA until recovery to ≤ Grade 1, then resume TUKYSA at the next lower dose level.
	Grade 4 ALT or AST (>20 × ULN) OR Grade 4 bilirubin (>10 × ULN)	Permanently discontinue TUKYSA.
	ALT or AST >3 × ULN AND Bilirubin >2 × ULN	Permanently discontinue TUKYSA.
Other adverse reactions	Grade 3	Hold TUKYSA until recovery to ≤ Grade 1, then resume TUKYSA at the next lower dose level.
	Grade 4	Permanently discontinue TUKYSA.

Grades based on National Cancer Institute Common Terminology Criteria for Adverse Events Version 4.03.

Please see additional Important Safety Information and the accompanying full Prescribing Information.

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Managing drug interactions

Drug interactions that affect TUKYSA

	Select examples[3]*	Clinical impact[1]	Management[1]
Strong CYP3A inducers	Carbamazepine, phenytoin, rifampin, St. John's wort	May reduce TUKYSA activity	Avoid concomitant use of TUKYSA with a strong CYP3A inducer.
Moderate CYP2C8 inducers	Rifampin	May reduce TUKYSA activity	Avoid concomitant use of TUKYSA with a moderate CYP2C8 inducer.
Strong or moderate CYP2C8 inhibitors	Clopidogrel (moderate), deferasirox (moderate), gemfibrozil (strong), teriflunomide (moderate)	May increase the risk of TUKYSA toxicity	Avoid concomitant use of TUKYSA with a strong CYP2C8 inhibitor. Increase monitoring for TUKYSA toxicity with moderate CYP2C8 inhibitors.

TUKYSA drug interactions that affect other drugs

	Select examples[3]*	Clinical impact[1]	Management[1]
CYP3A substrates	Atorvastatin, colchicine, darunavir, itraconazole, quetiapine, rivaroxaban, simvastatin, sirolimus	May increase CYP3A substrate toxicity	Avoid concomitant use of TUKYSA with CYP3A substrates, where minimal concentration changes may lead to serious or life-threatening toxicities. If unavoidable, decrease the CYP3A substrate dosage in accordance with approved product labeling.
P-gp substrates	Digoxin, fexofenadine	May increase P-gp substrate toxicity	Consider reducing the dosage of P-gp substrates, where minimal concentration changes may lead to serious or life-threatening toxicities.

*This is not an exhaustive list and is intended only to complement, not replace, clinical judgment during treatment of patients with TUKYSA. Please refer to the FDA website for more examples.
P-gp = P-glycoprotein.

Please see additional Important Safety Information and the accompanying full Prescribing Information.

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Your patients may find these resources helpful as they receive treatment with TUKYSA

TUKYSA Patient Brochure

- Provides your patients with a guide to treatment with TUKYSA

Treatment Tracker

- Tips and a calendar to help your patients start and stay on the TUKYSA treatment regimen

Frequently Asked Questions

- Answers to frequently asked questions about treatment with TUKYSA

Download materials from
www.TUKYSAhcp.com/mcrc/resources-and-support
or talk to your Pfizer Account Manager

References

1. TUKYSA. Prescribing information. Seagen Inc.; 2023. **2.** Strickler JH, Cercek A, Siena S, et al; MOUNTAINEER investigators. Tucatinib plus trastuzumab for chemotherapy-refractory, HER2-positive, *RAS* wild-type unresectable or metastatic colorectal cancer (MOUNTAINEER): a multicentre, open-label, phase 2 study. *Lancet Oncol*. 2023;24(5):496-508. doi:10.1016/S1470-2045(23)00150-X **3.** Food and Drug Administration. For healthcare professionals: FDA's examples of drugs that interact with CYP enzymes and transporter systems. Updated June 24, 2024. Accessed July 15, 2024. https://www.fda.gov/drugs/drug-interactions-labeling/healthcare-professionals-fdas-examples-drugs-interact-cyp-enzymes-and-transporter-systems

Please see additional Important Safety Information and the accompanying full Prescribing Information.

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