TUKYSA®
tucatinib
50 mg | 150 mg tablets

TUKYSA + trastuzumab + capecitabine

DOSING AND ADMINISTRATION GUIDE

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

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

Indication

TUKYSA is indicated in combination with trastuzumab and capecitabine for treatment of adult patients with advanced unresectable or metastatic HER2-positive breast cancer, including patients with brain metastases, who have received one or more prior anti-HER2-based regimens in the metastatic setting.

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 and capecitabine were diarrhea, vomiting, nausea, abdominal pain, and seizure.

The most common adverse reactions in ≥20% of patients who received TUKYSA in combination with trastuzumab and capecitabine were diarrhea, palmar-plantar erythrodysesthesia, nausea, hepatotoxicity, vomiting, stomatitis, decreased appetite, anemia, and rash.

MBC = metastatic breast cancer.

Please see additional 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 HER2CLIMB, when TUKYSA was given in combination with trastuzumab and capecitabine, 81% of patients who received TUKYSA experienced diarrhea, including 0.5% with Grade 4 and 12% with Grade 3. Both patients who developed Grade 4 diarrhea subsequently died, with diarrhea as a contributor to death. Median time to onset of the first episode of diarrhea was 12 days and the median time to resolution was 8 days. Diarrhea led to TUKYSA dose reductions in 6% of patients and TUKYSA discontinuation in 1% of patients. Prophylactic use of antidiarrheal treatment was not required on HER2CLIMB.

- **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 HER2CLIMB, 8% of patients who received TUKYSA had an ALT increase >5 x ULN, 6% had an AST increase >5 x ULN, and 1.5% had a bilirubin increase >3 x ULN (Grade ≥3). Hepatotoxicity led to TUKYSA dose reductions in 8% of patients and TUKYSA discontinuation in 1.5% 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

In HER2CLIMB, serious adverse reactions occurred in 26% of patients who received TUKYSA; the most common (in ≥2% of patients) were diarrhea (4%), vomiting (2.5%), nausea (2%), abdominal pain (2%), and seizure (2%). Fatal adverse reactions occurred in 2% of patients who received TUKYSA including sudden death, sepsis, dehydration, and cardiogenic shock.

Adverse reactions led to treatment discontinuation in 6% of patients who received TUKYSA; the most common (in ≥1% of patients) were hepatotoxicity (1.5%) and diarrhea (1%). Adverse reactions led to dose reduction in 21% of patients who received TUKYSA; the most common (in ≥2% of patients) were hepatotoxicity (8%) and diarrhea (6%).

The most common adverse reactions in patients who received TUKYSA (≥20%) were diarrhea, palmar-plantar erythrodysesthesia, nausea, hepatotoxicity, vomiting, stomatitis, decreased appetite, anemia, and rash.

Lab Abnormalities

In HER2CLIMB, Grade ≥3 laboratory abnormalities reported in ≥5% of patients who received TUKYSA were decreased phosphate, increased ALT, decreased potassium, and increased AST.

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 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 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 toxicity.

Use in Specific Populations

- **Lactation:** Advise women not to breastfeed while taking TUKYSA and for 1 week after the last dose.
- **Renal Impairment:** Use of TUKYSA in combination with capecitabine and trastuzumab is not recommended in patients with severe renal impairment (CLcr < 30 mL/min), because capecitabine is contraindicated in patients with severe renal impairment.
- **Hepatic Impairment:** Reduce the dose of TUKYSA for patients with severe (Child-Pugh C) hepatic impairment.

Please see the accompanying full Prescribing Information.

TUKYSA® tucatinib
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Getting started with TUKYSA[1]

TUKYSA is an oral medication taken twice a day, every day, as part of a regimen containing trastuzumab and capecitabine

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

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 OR subcutaneous dosing: 600 mg	Every 21 days
Capecitabine* 1000 mg/m^2 orally, twice daily, taken within 30 minutes after a meal and may be taken at the same time as TUKYSA	Repeat 14 days of treatment with 7 days off treatment

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

Monitor ALT, AST, and bilirubin before starting treatment, 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 of TUKYSA 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

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

ALT = alanine aminotransferase; AST = aspartate aminotransferase; CYP = cytochrome P450.

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

TUKYSA® tucatinib 50 mg | 150 mg tablets

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

Dosage forms 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 Important Safety Information and the accompanying full Prescribing Information.

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Adverse reactions in HER2CLIMB

Adverse reactions (≥10%) in patients who received TUKYSA and with a difference between arms of ≥5% compared to placebo in HER2CLIMB[1]

	Placebo + trastuzumab + capecitabine (n = 197)			TUKYSA + trastuzumab + capecitabine (n = 404)		
	All grades (%)	Grade 3 (%)	Grade 4 (%)	All grades (%)	Grade 3 (%)	Grade 4 (%)
Gastrointestinal disorders						
Diarrhea	53	9	0	81	12	0.5
Nausea	44	3	0	58	3.7	0
Vomiting	25	3.6	0	36	3	0
Stomatitis*	21	0.5	0	32	2.5	0
Skin and subcutaneous tissue disorders						
PPE syndrome	53	9	0	63	13	0
Rash†	15	0.5	0	20	0.7	0
Hepatobiliary disorders						
Hepatotoxicity‡	24	3.6	0	42	9	0.2
Metabolism and nutrition disorders						
Decreased appetite	20	0	0	25	0.5	0
Blood and lymphatic system disorders						
Anemia§	13	2.5	0	21	3.7	0
Musculoskeletal and connective tissue disorders						
Arthralgia	4.6	0.5	0	15	0.5	0
Investigations						
Creatinine increased‖	1.5	0	0	14	0	0
Weight decreased	6	0.5	0	13	1	0
Nervous system disorders						
Peripheral neuropathy¶	7	1	0	13	0.5	0
Respiratory, thoracic, and mediastinal disorders						
Epistaxis	5	0	0	12	0	0

Serious adverse reactions occurring in ≥2% of patients in the TUKYSA arm#

- **Any reaction:** 26% (diarrhea, 4.0%; vomiting, 2.5%; nausea, 2.0%; abdominal pain, 2.0%; seizure, 2.0%)[1]
- **Fatal reactions:** 2%, including sudden death, sepsis, dehydration, and cardiogenic shock[1,2]
- Laboratory abnormalities (≥20%) worsening from baseline in patients who received TUKYSA and with a difference of ≥5% compared to placebo in HER2CLIMB were decreased hemoglobin (59% vs 51% [Grade ≥3, 3.3% vs 1.5%]), decreased phosphate (57% vs 45%), increased bilirubin (47% vs 30%), increased ALT (46% vs 27%), increased AST (43% vs 25%), decreased magnesium (40% vs 25%), decreased potassium (36% vs 31%), increased creatinine (33% vs 6%), decreased sodium (28% vs 23%), and increased alkaline phosphatase (26% vs 17%)[1]

*Stomatitis includes stomatitis, oropharyngeal pain, oropharyngeal discomfort, mouth ulceration, oral pain, lip ulceration, glossodynia, tongue blistering, lip blister, oral dysesthesia, tongue ulceration, and aphthous ulcer.[1]
†Rash includes rash maculo-papular, rash, dermatitis acneiform, erythema, rash macular, rash papular, rash pustular, rash pruritic, rash erythematous, skin exfoliation, urticaria, dermatitis allergic, palmar erythema, plantar erythema, skin toxicity, and dermatitis.[1]
‡Hepatotoxicity includes hyperbilirubinemia, blood bilirubin increased, bilirubin conjugated increased, alanine aminotransferase increased, transaminases increased, hepatotoxicity, aspartate aminotransferase increased, liver function test increased, liver injury, and hepatocellular injury.[1]
§Anemia includes anemia, hemoglobin decreased, and normocytic anemia.[1]
‖Due to inhibition of renal tubular transport of creatinine without affecting glomerular function.[1]
¶Peripheral neuropathy includes peripheral sensory neuropathy, neuropathy peripheral, peripheral motor neuropathy, and peripheral sensorimotor neuropathy.[1]
#An adverse reaction is considered serious if it results in death, is life-threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in disability, or causes a congenital anomaly/birth defect.[3]
PPE = palmar-plantar erythrodysesthesia.

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

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Monitoring for adverse reactions

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[1]

Diarrhea

- TUKYSA can cause severe diarrhea, including dehydration, hypotension, acute kidney injury, and death[1]
  - Median time to onset (any grade) was 12 days[1]
  - Median time to resolution was 8 days[1]
  - Median duration of antidiarrheal use was 3 days for each 21-day repeating regimen[2]
- Diarrhea led to TUKYSA dose reductions in 6% of patients and TUKYSA permanent discontinuation in 1% of patients[1]
- 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[1]
- 81% of patients who received TUKYSA experienced diarrhea, including 0.5% with Grade 4 and 12% with Grade 3. Both patients who developed Grade 4 diarrhea subsequently died, with diarrhea as a contributor to death[1]

See page 7 for dose modifications to manage diarrhea and hepatotoxicity

Hepatotoxicity[1]

- TUKYSA can cause severe hepatotoxicity
  - 8% of patients who received TUKYSA had an ALT increase >5 x ULN, 6% had an AST increase >5 x ULN, and 1.5% had a bilirubin increase >3 x ULN (Grade ≥3)
- Hepatotoxicity led to TUKYSA dose reductions in 8% of patients and TUKYSA permanent discontinuation in 1.5% of patients
- Monitor ALT, AST, and bilirubin prior to starting treatment with TUKYSA, every 3 weeks during treatment, and as clinically indicated. Based on the severity of hepatotoxicity, interrupt dose, then dose reduce or permanently discontinue

Monitor ALT, AST, and bilirubin before starting treatment with TUKYSA, every 3 weeks during treatment, and as clinically indicated[1]

Permanent discontinuation in HER2CLIMB[1,2,4]

Agent discontinued	Placebo + trastuzumab + capecitabine (n = 197)	TUKYSA + trastuzumab + capecitabine (n = 404)
TUKYSA or placebo	3%	6%
Trastuzumab	3%	5%
Capecitabine	9%	10%

Dose reductions and permanent discontinuation[1]

- Adverse reactions leading to permanent discontinuation of TUKYSA in ≥1% of patients were hepatotoxicity (1.5%) and diarrhea (1%)
- Adverse reactions leading to dose reduction of TUKYSA in ≥2% of patients were hepatotoxicity (8%) and diarrhea (6%)

ULN = upper limit of normal.

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

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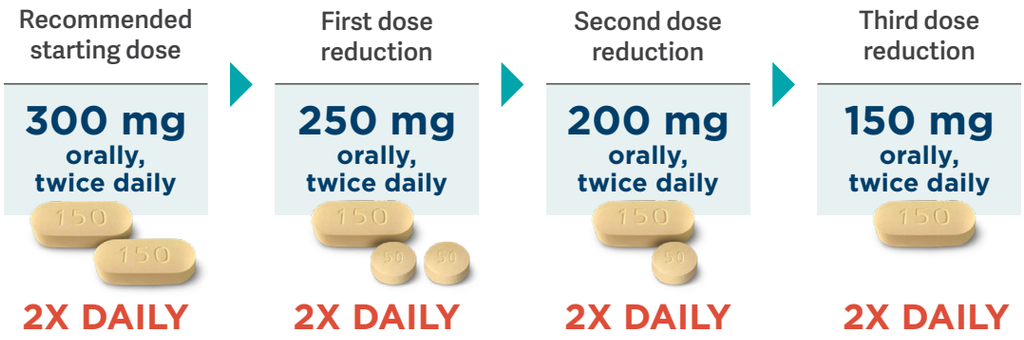
Modifying the TUKYSA dose[1]

Some patients may require dose modifications or permanent discontinuation of therapy to manage adverse reactions. In HER2CLIMB, 21% of patients had their TUKYSA dose modified and 6% permanently discontinued TUKYSA.

Reduce TUKYSA in increments of 50 mg to manage adverse reactions



- Permanently discontinue TUKYSA in patients unable to tolerate 150 mg orally, twice daily

For modifications to administration of trastuzumab and dosing of capecitabine, consult the Prescribing Information for each agent

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	
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 Important Safety Information and the accompanying full Prescribing Information.

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Managing drug interactions

Drug interactions that affect TUKYSA

	Select examples[5]*	Clinical impact[1]	Management[1]
Strong CYP3A inducers	Carbamazepine, phenytoin, rifampin, St. John's wort	May reduce TUKYSA activity	Avoid prescribing TUKYSA with a strong CYP3A inducer.
Moderate CYP2C8 inducers	Rifampin	May reduce TUKYSA activity	Avoid prescribing TUKYSA with a moderate CYP2C8 inducer.
Strong or moderate CYP2C8 inhibitors	Clopidogrel (moderate), deferasirox (moderate), gemfibrozil (strong), teriflunomide (moderate)	Strong CYP2C8 inhibitors may increase the risk of TUKYSA toxicity	Avoid prescribing TUKYSA with a strong CYP2C8 inhibitor. Increase monitoring for TUKYSA toxicity with a moderate CYP2C8 inhibitor.

TUKYSA drug interactions that affect other drugs

	Select examples[5]*	Clinical impact[1]	Management[1]
CYP3A substrates	Atorvastatin, colchicine, darunavir, itraconazole, quetiapine, rivaroxaban, simvastatin, sirolimus	May increase CYP3A substrate toxicity	Avoid prescribing 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.

Updated: July 17, 2024

*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.

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
or talk to your Pfizer Account Manager

References: 1. TUKYSA. Prescribing information. Seagen Inc.; 2023. **2.** Murthy RK, Loi S, Okines A, et al. Tucatinib, trastuzumab, and capecitabine for HER2-positive metastatic breast cancer. *N Engl J Med*. 2020;382(7):597-609. doi:10.1056/NEJMoa1914609 **3.** Food and Drug Administration. What is a serious adverse event? Updated May 18, 2023. Accessed April 16, 2024. https://www.fda.gov/safety/reporting-serious-problems-fda/what-serious-adverse-event **4.** Okines A, Paplomata E, Wahl T, et al. Management of adverse events in patients with HER2+ metastatic breast cancer treated with tucatinib, trastuzumab, and capecitabine (HER2CLIMB). Poster presented at: American Society of Clinical Oncology Annual Meeting; May 29-31, 2020. **5.** 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

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Pfizer Oncology

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