Tukysa (tucatinib)

NEW PRODUCT SLIDESHOW

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Introduction

- **Brand name:** Tukysa
- **Generic name:** Tucatinib
- **Pharmacologic class:** Tyrosine kinase inhibitor
- **Strength and Formulation:** 50mg, 150mg; tablets
- **Manufacturer:** Seattle Genetics, Inc.
- **How supplied:** Tabs 50mg—60; 150mg—60, 120
- **Legal Classification:** Rx

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Tukysa


NDC 51144-002-60
Rx Only
TUKYSA™
(tucatinib) tablets
150 mg*
Attention: Dispense and store Tukysa in original container to protect from moisture.
SeattleGenetics
60 Tablets

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Indication

- 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

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Dosage and Administration

- Swallow whole
- **300mg twice daily** (approx. 12hrs apart) in combination with trastuzumab and capecitabine until disease progression or unacceptable toxicity
- **Concomitant strong CYP2C8 inhibitors** (if unavoidable): 100mg twice daily
- **Severe hepatic impairment** (Child-Pugh C): 200mg twice daily

Dosage and Administration

Dosage Modifications for Adverse Reactions

Dose Reduction	Recommended Tukysa Dosage
First	250mg twice daily
Second	200mg twice daily
Third	150mg twice daily

Permanently discontinue in patients unable to tolerate 150mg twice daily

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Dosage and Administration

Recommended Dosage Modifications for Adverse Reactions

Adverse Reaction	Severity	Dosage Modification
Diarrhea	Grade 3 without antidiarrheal treatment	Initiate or intensify appropriate medical therapy; hold Tukysa until recovery to ≤ Grade 1, then resume at same dose level
	Grade 3 with anti-diarrheal treatment	Initiate or intensify appropriate medical therapy; hold Tukysa until recovery to ≤ Grade 1, then resume at next lower dose level.
	Grade 4	Permanently discontinue

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Dosage and Administration

Recommended Dosage Modifications for Adverse Reactions

Adverse Reaction	Severity	Dosage Modification
Hepatotoxicity	Grade 2 bilirubin (>1.5 to 3 × ULN)	Hold Tukysa until recovery to ≤ Grade 1, then resume at 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 at next lower dose level
	Grade 4 ALT or AST (>20 × ULN) **OR** Grade 4 bilirubin (>10 × ULN)	Permanently discontinue
	ALT or AST >3 × ULN **AND** Bilirubin >2 × ULN	Permanently discontinue

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Dosage and Administration

Recommended Dosage Modifications for Adverse Reactions

Adverse Reaction	Severity	Dosage Modification
Other adverse reactions	Grade 3	Hold Tukysa until recovery to ≤ Grade 1, then resume at next lower dose level
	Grade 4	Permanently discontinue

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Considerations for Special Populations

- **Pregnancy:** may cause fetal harm
- **Nursing mothers**: not recommended during treatment and for at least 1 week after last dose
- **Females of reproductive potential**: verify pregnancy status prior to treatment; use effective contraception during and for at least 1 week after last dose; may impair fertility
- **Males of reproductive potential**: use effective contraception during and for at least 1 week after last dose; may impair fertility
- **Pediatric**: not established
- **Geriatrics**: no overall differences in effectiveness; too few patients 75 years and older to assess differences

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Considerations for Special Populations

- **Hepatic impairment**: increased exposure in patients with severe impairment; reduce dose (see Dosing)
- **Renal impairment**: not recommended in patients with severe impairment (CrCl<30mL/min) because capecitabine is contraindicated in these patients

Warnings/Precautions

- Risk of severe diarrhea (including dehydration, hypotension, acute kidney injury, death); give antidiarrheal if occurs
- Perform diagnostic tests as needed to exclude other causes of diarrhea
- Risk of severe hepatotoxicity
- Monitor liver function tests prior to initiation, every 3 weeks during, then as clinically indicated
- Embryo-fetal toxicity

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Interactions

- Potentiated by **strong CYP2C8 inhibitors** (eg, gemfibrozil); avoid concomitant use; reduce dose if unavoidable (see Dosing); monitor frequently, and for moderate CYP2C8 inhibitors
- Antagonized by **strong CYP3A or moderate CYP2C8 inducers** (eg, rifampin); avoid
- Potentiates CYP3A substrates (eg, midazolam); avoid concomitant use; decrease CYP3A substrate dose if unavoidable
- Potentiates **P-gp substrates** (eg, digoxin); consider dose reduction of P-gp substrate

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Adverse Reactions

- **Most frequent** (≥20%): diarrhea, palmar-plantar erythrodysesthesia, nausea, fatigue, hepatotoxicity, vomiting, stomatitis, decreased appetite, abdominal pain, headache, anemia, rash

Mechanism of Action

- Tucatinib is a tyrosine kinase inhibitor of HER2
- *In vit*ro, tucatinib inhibits phosphorylation of HER2 and HER3, resulting in inhibition of downstream MAPK and AKT signaling and cell proliferation, and showed anti-tumor activity in HER2 expressing tumor cells
- *In vivo*, tucatinib inhibited the growth of HER2 expressing tumors
- The combination of tucatinib and trastuzumab showed increased anti-tumor activity *in vitro* and *in vivo* compared to either drug alone

Clinical Trials

- Efficacy of Tukysa in combination with trastuzumab and capecitabine evaluated in 612 patients in a randomized, double-blind, placebo-controlled trial
- Patients were required to have HER2-positive, unresectable locally advanced or metastatic breast cancer, with or without brain metastases, and prior treatment with trastuzumab, pertuzumab, and ado-trastuzumab emtansine (T-DM1) separately or in combination, in the neoadjuvant, adjuvant or metastatic setting

Clinical Trials

- **Patient demographics**
  - Median age: 54 years; 116 patients were age 65 and older
  - Majority were white (73%) and female (99%)
  - 51% had ECOG performance status of 1
  - 60% had estrogen and/or progesterone receptor-positive disease
  - 48% had a presence or history of brain metastases; of these 23% had untreated brain metastases
  - 40% had treated but stable brain metastases and 37% had treated but radiographically progressing brain metastases
  - 74% had visceral metastases
  - Patients had received a median of 4 prior lines of systemic therapy and a median of 3 prior lines of systemic therapy in the metastatic setting
  - All patients received prior trastuzumab and T-DM1 and all but 2 patients had prior pertuzumab

Clinical Trials

- Patients received Tukysa 300mg or placebo orally twice daily with a trastuzumab loading dose of 8mg/kg on Day 1 of Cycle 1 if needed and then a maintenance dose of 6mg/kg on Day 1 of every 21-day cycle thereafter and capecitabine 1000mg/m^2 orally twice daily on Days 1 through 14 of every 21-day cycle
- An alternate trastuzumab dosing regimen was 600mg administered subcutaneously on Day 1 of every 21-day cycle
- Patients were treated until disease progression or unacceptable toxicity

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Clinical Trials

- Tumor assessments, including brain-MRI in patients with presence or history of brain metastases at baseline, occurred every 6 weeks for the first 24 weeks and every 9 weeks thereafter
- **Primary end point**: progression-free survival (PFS) in the first 480 randomized patients assessed by blinded independent central review using Response Evaluation Criteria in Solid Tumors (RECIST) v1.1
- Additional efficacy outcome measures included overall survival (OS), PFS among patients with a history or presence of brain metastases ($PFS_{BrainMets}$), and confirmed objective response rate (ORR)

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Clinical Trials

Results

- **PFS:** 7.8 months (95% CI, 7.5-9.6) with Tukysa vs 5.6 months (95% CI, 4.2-7.1) with placebo
  - Hazard ratio (HR): 0.54 (95% CI, 0.42-0.71); *P* <.00001
- **OS:** 21.9 months (95% CI, 18.3-31.0) with Tukysa vs 17.4 months (95% CI, 13.6-19.9) with placebo
  - HR: 0.66 (95% CI, 0.50-0.87); *P* =.00480
- **$PFS_{BrainMets}$:** 7.6 months (95% CI, 6.2-9.5) with Tukysa vs 5.4 months (95% CI, 4.1-5.7) with placebo
  - HR: 0.48 (95% CI, 0.34-0.69); *P* <.00001
- **Confirmed ORR for patients with measurable disease:** 40.6% with Tukysa vs 22.8% with placebo
- **Duration of response:** 8.3 months with Tukysa vs 6.3 months with placebo

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New Product Monograph

- For more information view the product monograph available at:

  https://www.empr.com/drug/tukysa/