

Composition:

Tykasa 50 Tablet: Each film coated tablet contains Tucatinib Hemithanolate INN equivalent to Tucatinib 50 mg.
Tykasa 150 Tablet: Each film coated tablet contains Tucatinib Hemithanolate INN equivalent to Tucatinib 150 mg.

Clinical Pharmacology:

Tucatinib is a tyrosine kinase inhibitor of HER2. In vitro, 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.

Indications:

Tucatinib is a kinase inhibitor 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.

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.

Dosage and Administration:

Recommended Dosage

Metastatic Breast Cancer: The recommended dosage of Tucatinib is 300 mg taken orally twice daily in combination with trastuzumab and capecitabine until disease progression or unacceptable toxicity.

Unresectable or Metastatic Colorectal Cancer: The recommended dosage of Tucatinib is 300 mg taken orally twice daily in combination with trastuzumab until disease progression or unacceptable toxicity. Patients are advised to swallow Tucatinib tablets whole and not to chew, crush, or split prior to swallowing. Patients are advised not to ingest tablet if it is broken, cracked, or not otherwise intact.

Patients are advised to take Tucatinib approximately 12 hours apart and at the same time each day with or without a meal.

When given in combination with Tucatinib, the recommended dosage of capecitabine is 1000 mg/m² orally twice daily taken within 30 minutes after a meal. Tucatinib and capecitabine can be taken at the same time.

Recommended Dose Reduction for Adverse Reactions:

Dose Reduction	Recommended Tucatinib Dosage
1 st Dose Reduction	250 mg orally twice daily
2 nd Dose Reduction	200 mg orally twice daily
3 rd Dose Reduction	150 mg orally twice daily

Permanently discontinue Tucatinib in patients unable to tolerate 150 mg orally twice daily.

Dosage Modifications for Severe Hepatic Impairment:

For patients with severe hepatic impairment (Child-Pugh C), reduce the recommended dosage to 200 mg orally twice daily.

Dosage Modifications for Concomitant Use with Strong CYP2C8 Inhibitors:

Avoid concomitant use of strong CYP2C8 inhibitors with Tucatinib. 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 Tucatinib dose that was taken prior to initiating the inhibitor.

Contraindications: None.

Warning and Precautions:

Diarrhea: Severe diarrhea, including dehydration, acute kidney injury, and death, has been reported. Patients are advised to administer antidiarrheal treatment as clinically indicated. Patients are advised to interrupt dose, then reduce dose, or permanently discontinue Tucatinib based on severity.

Hepatotoxicity: Severe hepatotoxicity has been reported on Tucatinib. Patients are advised to monitor ALT, AST and bilirubin prior to starting Tucatinib, every 3 weeks during treatment and as clinically indicated. Interrupt dose, then reduce dose, or permanently discontinue Tucatinib based on severity.

Embryo-Fetal Toxicity: Tucatinib can cause fetal harm. Patients are advised of potential risk to a fetus and to use effective contraception.

Adverse Reactions:

The most common adverse reactions (≥20%) with Tucatinib in combination with trastuzumab and capecitabine in patients with metastatic breast cancer are diarrhea, palmar-plantar erythrodysesthesia, nausea, hepatotoxicity, vomiting, stomatitis, decreased appetite, anemia, and rash.

The most common adverse reactions (≥20%) with Tucatinib in combination with trastuzumab in patients with unresectable or metastatic colorectal cancer are diarrhea, fatigue, rash, nausea, abdominal pain, infusion related reactions, and pyrexia.

Use In Special Population:

Pregnancy: Advise pregnant women and females of reproductive potential of the potential risk to the fetus.

Lactation: There are no data on the presence of Tucatinib or its metabolites in human or animal milk or its effects on the breastfed child or on milk production. Because of the potential for serious adverse reactions in a breastfed child, advise women not to breastfeed during treatment with Tucatinib and for 1 week after the last dose.

Females and males of reproductive potential: Tucatinib can cause fetal harm when administered to a pregnant woman.

Pregnancy Testing: Verify the pregnancy status of females of reproductive potential prior to initiating treatment with Tucatinib.

Contraception:

Females: Advise females of reproductive potential to use effective contraception during treatment with Tucatinib and for 1 week after the last dose.

Males: Advise male patients with female partners of reproductive potential to use effective contraception during treatment with Tucatinib and for 1 week after the last dose.

Infertility: Based on findings from animal studies, Tucatinib may impair male and female fertility.

Pediatric use: The safety and effectiveness of Tucatinib in pediatric patients have not been established.

Geriatric use: In HER2CLIMB, 82 patients who received Tucatinib were ≥ 65 years, of whom 8 patients were ≥ 75 years. The incidence of serious adverse reactions in those receiving Tucatinib was 34% in patients ≥ 65 years compared to 24% in patients <65 years. The most frequent serious adverse reactions in patients ≥65 years who received Tucatinib were diarrhea (9%), vomiting (6%), and nausea (5%).

Renal impairment: The use of Tucatinib in combination with capecitabine and trastuzumab is not recommended in patients with severe renal impairment (creatinine clearance [CL_{Cr}]: < 30 mL/min estimated by Cockcroft-Gault Equation), because capecitabine is contraindicated in patients with severe renal impairment. No dose adjustment is recommended for patients with mild or moderate renal impairment (CL_{Cr}: 30 to 89 mL/min).

Hepatic Impairment: Tucatinib exposure is increased in patients with severe hepatic impairment (Child-Pugh C). Reduce the dose of Tucatinib for patients with severe (Child-Pugh C) hepatic impairment. No dose adjustment for Tucatinib is required for patients with mild (Child-Pugh A) or moderate (Child-Pugh B) hepatic impairment.

Drug Interaction:

Effects of Other Drugs on Tucatinib:

Strong CYP3A Inducers or Moderate CYP2C8 Inducers:

Concomitant use of Tucatinib with a strong CYP3A or moderate CYP2C8 inducer decreased Tucatinib plasma concentrations. Avoid concomitant use of Tucatinib with a strong CYP3A inducer or a moderate CYP2C8 inducer.

Strong or Moderate CYP2C8 Inhibitors: Concomitant use of Tucatinib with a strong CYP2C8 inhibitor increased Tucatinib plasma concentrations. Avoid concomitant use of Tucatinib with a strong CYP2C8 inhibitor. Increase monitoring for Tucatinib toxicity with moderate CYP2C8 inhibitors.

Effects of Tucatinib on Other Drugs:

CYP3A Substrates: Concomitant use of Tucatinib with a CYP3A substrate increased the plasma concentrations of CYP3A substrate, which may increase the toxicity associated with a CYP3A substrate. Avoid concomitant use of Tucatinib with CYP3A substrates, where minimal concentration changes may lead to serious or life-threatening toxicities. If concomitant use is unavoidable, decrease the CYP3A substrate dosage in accordance with approved product labeling.

P-glycoprotein (P-gp) Substrates: Concomitant use of Tucatinib with a P-gp substrate increased the plasma concentrations of P-gp substrate, which 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.

Overdose:

There is no specific antidote, and the benefit of haemodialysis in the treatment of Tucatinib overdose is unknown. In the event of an overdose, treatment with tucatinib should be withheld and general supportive measures should be applied.

Storage:

Store in a cool & dry place below 30° C, protect from light. Keep out of the reach of children.

Packaging:

Tykasa 50 Tablet: Each box contains 30 Tablets & one packet silica gel in a sealed HDPE container.
Tykasa 150 Tablet: Each box contains 28 Tablets & one packet silica gel in a sealed HDPE container.