

COMPOSITION

TUCAXEN 50 TABLET: Each film-coated tablet contains Tucatinib INN 50 mg.

TUCAXEN 150 TABLET: Each film-coated tablet contains Tucatinib INN 150 mg.

PHARMACOLOGY

Mechanism of Action

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.

Pharmacodynamics

Exposure Response Relationship

Tucatinib exposure-response relationships and the time course of pharmacodynamics response have not been fully characterized.

Cardiac Electrophysiology

No large mean increase in QTc (i.e., > 20 ms) was detected following treatment with Tucatinib at the recommended dose of 300 mg taken orally twice daily.

Pharmacokinetics

Tucatinib AUC0-INF and Cmax increases proportionally over a dosage range from 50 mg to 300 mg (0.17 to 1 times the approved recommended dosage). Tucatinib exhibited 1.7-fold accumulation for AUC and 1.5-fold accumulation for Cmax following administration of Tucatinib 300 mg twice daily for 14 days. Time to steady state was approximately 4 days.

Absorption

The median time to peak plasma concentration of Tucatinib was approximately 2 hours (range 1 to 4 hours).

Effects of Food

Following administration of a single oral dose of Tucatinib in 11 subjects after a high-fat meal (approximately 58% fat, 26% carbohydrate, and 16% protein), the mean AUC0-INF increased by 1.5-fold, the Tmax shifted from 1.5 hours to 4 hours, and Cmax was unaltered. The effect of food on the pharmacokinetics of tucatinib was not clinically meaningful.

Distribution

The geometric mean (CV%) apparent volume of distribution of tucatinib was approximately 1670 L (66%). The plasma protein binding was 97.1% at clinically relevant concentrations.

Elimination

The geometric mean (CV%) half-life of tucatinib was approximately 8.5 (21%) hours and apparent clearance was 148 L/h (55%).

Metabolism

Tucatinib is metabolized primarily by CYP2C8 and to a lesser extent via CYP3A.

Excretion

Following a single oral dose of 300 mg radiolabeled Tucatinib, approximately 86% of the total radiolabeled dose was recovered in feces (16% of the administered dose as unchanged tucatinib) and 4.1% in urine with an overall total recovery of 90% within 13 days post-dose. In plasma, approximately 76% of the plasma radioactivity was unchanged, 19% was attributed to identified metabolites, and approximately 5% was unassigned.

INDICATION

Tucatinib 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.

DOSAGE AND ADMINISTRATION

Recommended Dosage

The recommended dosage of Tucatinib is 300 mg taken orally twice daily in combination with trastuzumab and capecitabine 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.

If the patient vomits or misses a dose of Tucatinib, Patients are advised to take the next dose at its usual scheduled time.

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.

Dosage Modifications for Adverse Reactions

Recommended Tucatinib Dose Reductions for Adverse Reactions

Dose Reduction	Recommended Tucatinib Dosage
First	250 mg orally twice daily
Second	200 mg orally twice daily
Third	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.

CONTRAINDICATION

None.

WARNING AND PRECAUTION

Diarrhea

Tucatinib can cause severe diarrhea including dehydration, hypotension, acute kidney injury, and death. In HER2CLIMB, 81% of patients who received Tucatinib experienced diarrhea, including 12% with Grade 3 diarrhea and 0.5% with Grade 4 diarrhea. Both patients who developed Grade 4 diarrhea subsequently died, with diarrhea as a contributor to death. The 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 dose reductions of Tucatinib in 6% of patients and discontinuation of Tucatinib in 1% of patients. Prophylactic use of antidiarrheal treatment was not required on HER2CLIMB.

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 reduce dose or permanently discontinue Tucatinib.

Hepatotoxicity

Tucatinib can cause severe hepatotoxicity .In HER2CLIMB, 8% of patients who received Tucatinib had an ALT increase > 5 × ULN, 6% had an AST increase > 5 × ULN, and 1.5% had a bilirubin increase > 3 × ULN (Grade ≥3). Hepatotoxicity led to dose reduction of Tucatinib in 8% of patients and discontinuation of Tucatinib in 1.5% of patients.

Monitor ALT, AST, and bilirubin prior to starting Tucatinib, every 3 weeks during treatment, and as clinically indicated. Based on the severity of hepatotoxicity, interrupt dose, then reduce dose or permanently discontinue Tucatinib.

Embryo-Fetal Toxicity

Based on findings from animal studies and its mechanism of action, Tucatinib can cause fetal harm when administered to a pregnant woman. In animal reproduction studies, administration of Tucatinib to pregnant rats and rabbits during organogenesis caused embryo-fetal mortality, reduced fetal weight and fetal abnormalities at maternal exposures ≥ 1.3 times the human exposure (AUC) at the recommended dose.

Advise pregnant women and females of reproductive potential of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with Tucatinib and for at least 1 week after the last dose. Advise male patients with female partners of reproductive potential to use effective contraception during treatment with Tucatinib and for at least 1 week after the last dose.

Tucatinib is used in combination with trastuzumab and capecitabine.

SIDE EFFECTS

The following clinically significant side effects are observed:

- Diarrhea
- Hepatotoxicity

The most common side effects in patients who received Tucatinib (≥20%) were diarrhea, palmar-plantar erythrodysesthesia, nausea, fatigue, hepatotoxicity, vomiting, stomatitis, decreased appetite, abdominal pain, headache, anemia, and rash.

DRUG INTERACTIONS

Effects of other Drugs on Tucatinib.

Drug Interactions that Affect Tucatinib

Drug Interactions that Affect Tucatinib	
Clinical Impact	Concomitant use of Tucatinib with a strong CYP3A or moderate CYP2C8 inducer decreased Tucatinib plasma concentrations, which may reduce Tucatinib activity.

