# TUCAXEN

Tucatinib 50 mg & 150 mg tablets

Everest

## 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. |

| Drug Interactions that Affect Tucatinib | |
|---|---|
| Management | Avoid concomitant use of Tucatinib with a strong CYP3A inducer or a moderate CYP2C8 inducer. |
| **Strong or Moderate CYP2C8 Inhibitors** | |
| Clinical Impact | Concomitant use of Tucatinib with a strong CYP2C8 inhibitor increased Tucatinib plasma concentrations, which may increase the risk of Tucatinib toxicity. |
| Management | 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**
**Tucatinib Drug Interactions that Affect Other Drugs**

| CYP3A Substrates | |
|---|---|
| Clinical Impact | 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. |
| Management | 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. |
| **CYP3A Substrates** | |
| Clinical Impact | 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. |
| Management | Consider reducing the dosage of P-gp substrates, where minimal concentration changes may lead to serious or life-threatening toxicities. |

**USE IN SPECIFIC POPULATIONS**

Pregnancy

*Risk Summary*

Tucatinib is used in combination with trastuzumab and capecitabine.

Based on findings in animals and its mechanism of action, Tucatinib can cause fetal harm when administered to a pregnant woman .There are no available human data on Tucatinib use in pregnant women to inform a drug-associated risk. Advise pregnant women and females of reproductive potential of the potential risk to the fetus.

The background risk of major birth defects and miscarriage for the indicated population is unknown.

Lactation

*Risk Summary*

Tucatinib is used in combination with trastuzumab and capecitabine.

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 at least 1 week after the last dose.

*Females and Males of Reproductive Potential*

Tucatinib can cause fetal harm when administered to a pregnant woman Tucatinib is used in combination with trastuzumab and capecitabine.

*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 at least 1 week after the last dose.

*Males*

Male patients with female partners of reproductive potential are advised to use effective contraception during treatment with Tucatinib and for at least 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 who received Tucatinib and ≥ 65 years were diarrhea (9%), vomiting (6%), and nausea (5%). There were no observed overall differences in the effectiveness of Tucatinib in patients ≥ 65 years compared to younger patients. There were too few patients ≥75 years to assess differences in effectiveness or safety.

*Renal Impairment*

The use of Tucatinib in combination with capecitabine and trastuzumab is not recommended in patients with severe renal impairment (CLcr < 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 (creatinine clearance [CLcr] 30 to 89 mL/min).

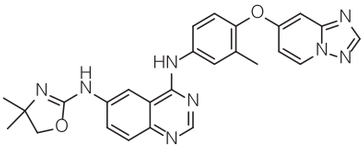
*Hepatic Impairment*

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.

**DESCRIPTION**

Tucatinib is a kinase inhibitor. The chemical name is (N4-(4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)-N6-(4,4-dimethyl-4,5-dihydrooxazol-2-yl)quinazoline-4,6-diamine. The molecular formula is C26H24N8O2 and the molecular weight is 480.52 g/mol. The chemical structure is as follows:



Specific Populations

Age (< 65 (n =211); ≥ 65 (n = 27)), albumin (25 to 52 g/L), creatinine clearance (creatinine clearance [CLcr] 60 to 89 mL/min (n = 89); CLcr 30 to 59 mL/min (n = 5)), body weight (41 to 138 kg), and race (White (n=168), Black (n=53), or Asian (n=10)) did not have a clinically meaningful effect on Tucatinib exposure.

**NONCLINICAL TOXICOLOGY**

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity studies have not been conducted with Tucatinib.

Tucatinib was not mutagenic in an in vitro bacterial reverse mutation (Ames) assay. Tucatinib was not clastogenic in either an in vitro chromosome aberration assay or an in vivo mouse bone marrow micronucleus assay.

Fertility studies in animals have not been conducted. In repeat-dose toxicity studies up to 13 weeks duration, decreased corpora lutea/corpus luteum cyst, increased interstitial cells of the ovary, atrophy of the uterus, and mucification of the vagina were observed in female rats at doses ≥ 6 mg/kg/day (approximately 0.1 times the human exposure at the recommended dose based on AUC). Atrophy and edema of the testes and oligospermia/-germ cell debris in the epididymides were observed in male rats at ≥ 120 mg/kg/day (approximately 13 times the human exposure at the recommended dose based on AUC).

**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.

**PHARMACEUTICAL INFORMATION**

**Storage**

Store below 25°C, in a cool and dry place. Keep away from light. Keep out of the reach of children.

**PHARMACEUTICAL INFORMATION**

**How Supplied**

TUCAXEN 50 TABLET: Each HDPE container contains 30 film-coated tablets (each tablet contains 50 mg Tucatinib) a silica gel desiccant and polyester coil with a child-resistant closure.

TUCAXEN 150 TABLET: Each HDPE container contains 30 film-coated tablets (each tablet contains 150 mg Tucatinib) a silica gel desiccant and polyester coil with a child-resistant closure.

Manufactured by
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