Drug Monograph

A - Drug Name

tucatinib

COMMON TRADE NAME(S): Tukysa™

back to top

B - Mechanism of Action and Pharmacokinetics

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

Absorption	Time to reach steady state	approximately 4 days
Distribution	PPB	97.1%
	Cross blood brain barrier?	Yes
Metabolism	Primarily by CYP2C8 and to a lesser extent by CYP3A	
	Active metabolites	Yes
	Inactive metabolites	Yes
Elimination	Feces	86% (16% unchanged drug)
	Urine	4%

Half-life	8.7 hours

back to top

C - Indications and Status

Health Canada Approvals:

- Breast cancer

Refer to the product monograph for a full list and details of approved indications

back to top

D - Adverse Effects

Emetogenic Potential: Minimal – No routine prophylaxis; PRN recommended

The following table lists adverse effects that occurred in a phase 3 trial of tucatinib versus placebo in combination with trastuzumab and capecitabine in patients with locally advanced unresectable or metastatic HER2- positive breast cancer, where incidences were ≥ 5% compared to placebo. Severe, life-threatening and post-marketing adverse effects from other sources are also included.

ORGAN SITE	SIDE EFFECT* (%)	ONSET**
Cardiovascular	Cardiotoxicity (rare)	E
Dermatological	Palmar-plantar erythrodysesthesia syndrome (PPES) (63%) (may be severe; 13%)	E
	Rash (20%)	E
Gastrointestinal	Anorexia, weight loss (25%)	E
	Diarrhea (81%) (may be severe; 12%)	E
	Mucositis (32%)	E
	Nausea, vomiting (58%) (generally mild)	E
General	Fatigue (45%)	E

Hematological	Anemia (21%)	E
	Hemorrhage (epistaxis 12%) (rare - rectal or vaginal)	E
Hepatobiliary	Hepatotoxicity (42%) (may be severe; 9%)	E
Infection	Infection (including septic stock - rare)	E
Metabolic / Endocrine	Hyperglycemia (rare)	E
	Hypoglycemia (rare)	E
Musculoskeletal	Musculoskeletal pain (15%)	E
Nervous System	Peripheral neuropathy (13%)	E
	Seizure (rare)	E D
Renal	Creatinine increased (14%)	E

* "*Incidence*" may refer to an absolute value or the higher value from a reported range.
"*Rare*" may refer to events with < 1% incidence, reported in post-marketing, phase 1 studies, isolated data or anecdotal reports.

** I = *immediate* (onset in hours to days) E = *early* (days to weeks)
D = *delayed* (weeks to months) L = *late* (months to years)

The most common side effects for tucatinib include diarrhea, palmar-plantar erythrodysesthesia syndrome (PPES), nausea, vomiting, fatigue, hepatotoxicity, mucositis, anorexia, weight loss, anemia, rash and musculoskeletal pain.

Severe **diarrhea** accompanied by dehydration, hypotension and acute kidney injury have been reported and may be fatal. The median onset of the first episode of diarrhea was 12 days and 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.

Hepatotoxicity, including severe hepatotoxicity, has been reported. The median time to onset of any grade ALT, AST, or bilirubin increase was 36 days with 84% of events resolving with a median time of 22 days. Hepatotoxicity led to dose reduction of tucatinib in 8% of patients and discontinuation of tucatinib in 1.5% of patients.

Increased serum creatinine due to inhibition of renal transport of creatinine without affecting glomerular function was reported. The mean increase in serum creatinine was 30% within the first 21 days of treatment. Increases persisted throughout treatment and were reversible upon treatment completion.

back to top

E - Dosing

Refer to protocol by which patient is being treated.

Screen for hepatitis B virus in all cancer patients starting systemic treatment. Refer to the hepatitis B virus screening and management guideline.

Adults:

- Patients with brain metastases requiring immediate local therapy should undergo local CNS directed therapy prior to being treated with tucatinib, if appropriate.

Oral: 300 mg BID continuously

(in combination with trastuzumab and capecitabine)

Refer to the CAPETUCA+TRAS Regimen Monograph for dosing information on trastuzumab and capecitabine

Dosage with Toxicity:

Dose Level	Tucatinib Dose (mg/BID)
0	300
-1	250
-2	200
-3	150
-4	Permanently discontinue

Toxicity	Grade	Tucatinib Dose*
Diarrhea	Grade 3, without antidiarrheal treatment	Initiate or intensify appropriate medical therapy. Hold until recovery to ≤ grade 1. Restart at same dose level.
	Grade 3, with antidiarrheal treatment	Initiate or intensify appropriate medical therapy. Hold until recovery to ≤ grade 1. Restart at 1 dose level ↓.
	Grade 4	Permanently discontinue
Hepatotoxicity	Bilirubin >1.5 to 3 x ULN	Hold until recovery to ≤ grade 1. Restart at same dose level.
	ALT or AST > 5 to 20 x ULN OR Bilirubin > 3 to 10 x ULN	Hold until recovery to ≤ grade 1. Restart at 1 dose level ↓.
	ALT or AST > 20 X ULN OR Bilirubin > 10 x ULN	Permanently discontinue
	ALT or AST > 3 x ULN AND Bilirubin > 2 x ULN	
Other Adverse Reactions	Grade 3	Hold until recovery to ≤ grade 1. Restart at 1 dose level ↓.
	Grade 4	Permanently discontinue

*Trastuzumab and capecitabine may also require dosage modification.

Dosage with Hepatic Impairment:

Baseline Liver Function	Tucatinib Dose
Child Pugh A or B	No dosage adjustment necessary
Child Pugh C	200 mg BID

Dosage with Renal Impairment:

Baseline Creatinine Clearance	Tucatinib Dose
CrCl ≥ 30 mL / min	No dosage adjustment necessary
CrCl < 30 mL / min	Use is not recommended. Tucatinib is used in combination with capecitabine and trastuzumab, and capecitabine is contraindicated in severe renal impairment.

Dosage in the elderly:

No dose adjustment is required in patients ≥ 65 years of age. No overall differences in effectiveness was observed in patients ≥ 65 years compared to younger patients. Patients ≥ 65 years were more likely to experience a serious adverse event such as diarrhea and vomiting and more likely to discontinue treatment compared to younger patients <65 years.

Children:

The safety and efficacy of tucatinib in pediatric patients has not been established.

back to top

F - Administration Guidelines

- Swallow tablets whole, do not chew, crush, or split prior to swallowing.
- Take approximately 12 hours apart at the same time each day with or without a meal.
- Tucatinib and capecitabine may be taken at the same time.
- If a dose is missed or vomited, administer the next dose at its usual time.
- Store original container at a controlled room temperature between 20ºC and 25ºC
- Protect from moisture.

back to top

G - Special Precautions

Contraindications:

- Patients who are hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container.

Other Warnings/Precautions:

- Use with caution in patients with known chronic liver disease, carriers of hepatitis B or C or with pre-existing liver function test abnormalities (total bilirubin > 1.5 × ULN, or AST/ALT > 2.5 × ULN, or AST/ALT > 5 × ULN if liver metastases were present) as they were excluded from clinical trials.
- Patients should exercise caution when driving or operating a vehicle or potentially dangerous machinery.

Other Drug Properties:

- Carcinogenicity: No information available

Pregnancy and Lactation:

- Clastogenicity: No
- Mutagenicity: No
- Teratogenicity: Documented in animals
- Pregnancy:
  - Tucatinib is not recommended for use in pregnancy. Adequate contraception should be used by patients and their partners during treatment, and for at least **1 week** after the last dose.
  - It is not known if tucatinib is present in semen. Patients should not donate or store semen during treatment and for at least **1 month** after the last dose.
- Breastfeeding:
  Breastfeeding is not recommended during treatment and for at least **1 week** after the last dose.
- Fertility effects: Probable
  Documented in animal studies

back to top

H - Interactions

Tucatinib is metabolized by and a reversible inhibitor of CYP2C8 and CYP3A. It is substrate of P-gp and BCRP and inhibits MATE1/MATE2-K mediated transport of metformin and OCT2/MATE1-mediated transport of creatinine.

No clinically significant drug interactions have been observed when tucatinib is co-administered with omeprazole.

AGENT	EFFECT	MECHANISM	MANAGEMENT
Moderate or Strong CYP2C8 Inducers (e.g. rifampin)	↓ tucatinib concentration and/or efficacy	↑ metabolism of tucatinib	Avoid concomitant use
Strong CYP3A4 inducers (i.e. phenytoin, rifampin etc)	↓ tucatinib concentration and/or efficacy	↑ metabolism of tucatinib	Avoid concomitant use
Moderate or Strong CYP2C8 Inhibitors (e.g. clopidogrel, gemfibrozil)	↑ tucatinib concentration and/or toxicity	↓ metabolism of tucatinib	Avoid concomitant use with strong inhibitors. If co-administration is unavoidable, reduce tucatinib starting dose to 100 mg twice daily and increase monitoring for tucatinib-related toxicity. After discontinuation of the strong CYP2C8 inhibitor for 3 elimination half-lives, resume tucatinib at dose taken prior to initiating the inhibitor. If co-administered with a moderate inhibitor, increase monitoring for toxicity.
CYP3A4 substrates (e.g. cyclosporine, pimozide, tacrolimus, triazolo-benzodiazepines,	↑ substrate concentration and/or toxicity	↓ metabolism of substrate	Avoid concomitant use. If co-administration is unavoidable, consider dose modification of CYP3A substrates with narrow therapeutic indices and/or

dihydropyridine calcium-channel blockers, certain HMG-CoA reductase inhibitors)			increased monitoring for potential adverse reactions.
P-glycoprotein substrates (i.e. verapamil, digoxin, morphine, ondansetron)	↑ substrate concentration and/or toxicity	↑ substrate exposure	Caution when co-administered with P-gp substrates with narrow therapeutic indices. Refer to the prescribing information of sensitive P-gp substrates for dose adjustment recommendations.

back to top

I - Recommended Clinical Monitoring

Treating physicians may decide to monitor more or less frequently for individual patients but should always consider recommendations from the product monograph.

Refer to the hepatitis B virus screening and management guideline for monitoring during and after treatment.

Recommended Clinical Monitoring

Monitor Type	Monitor Frequency
CBC	Baseline and as clinically indicated
Liver function tests	Baseline, every 3 weeks during treatment and as clinically indicated
Renal function tests	Baseline and as clinically indicated
Clinical toxicity assessment for fatigue, gastrointestinal effects, cutaneous reactions, infection, anemia, bleeding, neuropathy or seizure	As clinically indicated

Grade toxicity using the current NCI-CTCAE (Common Terminology Criteria for Adverse Events) version

back to top

J - Supplementary Public Funding

Exceptional Access Program (EAP Website)

- tucatinib - in combination with trastuzumab and capecitabine for advanced breast cancer, according to clinical criteria

back to top

K - References

Murthy RK, Loi S, Okines A, et al. Tucatinib, trastuzumab, and capecitabine for HER2-positive metastatic breast cancer. N Engl J Med 2020; 382:597-609.

Product Monograph: Tukysa™ (Tucatinib). McKesson Specialty Distribution Inc., June 2020.

February 2025 Updated Pregnancy and Lactation section

back to top

L - Disclaimer

Refer to the New Drug Funding Program or Ontario Public Drug Programs websites for the most up-to-date public funding information.

The information set out in the drug monographs, regimen monographs, appendices and symptom management information (for health professionals) contained in the Drug Formulary (the "Formulary") is intended for healthcare providers and is to be used for informational purposes only. The information is not intended to cover all possible uses, directions, precautions, drug interactions or adverse effects of a particular drug, nor should it be construed to indicate that use of a particular drug is safe, appropriate or effective for a given condition. The information in the Formulary is not intended to constitute or be a substitute for medical advice and should not be relied upon in any such regard. All uses of the Formulary are subject to clinical judgment and actual prescribing patterns may not follow the information provided in the Formulary.

The format and content of the drug monographs, regimen monographs, appendices and symptom management information contained in the Formulary will change as they are reviewed and revised on a periodic basis. The date of last revision will be visible on each page of the monograph and regimen. Since standards of usage are constantly evolving, it is advised that the Formulary not be used as the sole source of information. It is strongly recommended that original references or product monograph be consulted prior to using a chemotherapy regimen for the first time.

Some Formulary documents, such as the medication information sheets, regimen information sheets and symptom management information (for patients), are intended for patients. Patients should always consult with their healthcare provider if they have questions regarding any information set out in the Formulary documents.

While care has been taken in the preparation of the information contained in the Formulary, such information is provided on an "as-is" basis, without any representation, warranty, or condition, whether express, or implied, statutory or otherwise, as to the information's quality, accuracy, currency, completeness, or reliability.

CCO and the Formulary's content providers shall have no liability, whether direct, indirect, consequential, contingent, special, or incidental, related to or arising from the information in the Formulary or its use thereof, whether based on breach of contract or tort (including negligence), and even if advised of the possibility thereof. Anyone using the information in the Formulary does so at his or her own risk, and by using such information, agrees to indemnify CCO and its content providers from any and all liability, loss, damages, costs and expenses (including legal fees and expenses) arising from such person's use of the information in the Formulary.

back to top