DRUG NAME: Tucatinib

SYNONYM(S): ONT-380[1]

COMMON TRADE NAME(S): TUKYSA®

CLASSIFICATION: molecular targeted therapy

Special pediatric considerations are noted when applicable, otherwise adult provisions apply.

MECHANISM OF ACTION:

Tucatinib is an orally administered reversible tyrosine kinase inhibitor that is highly selective for the human epidermal growth factor receptor 2 (HER2). Tucatinib inhibits phosphorylation of HER2 and HER3 *in vitro*, resulting in inhibition of downstream cell signaling and proliferation, and induces cell death in HER2 expressing tumour lines. *In vivo*, tucatinib inhibits the growth of HER2 expressing tumours. Tucatinib is over 1000-fold more selective for HER2 compared to epidermal growth factor receptor (EGFR [HER1]).[1-3]

PHARMACOKINETICS:

Oral Absorption	T_{max} = 2 hours; time to steady state = 4 days; no clinically meaningful effect of food on pharmacokinetics	
Distribution	highly protein bound	
	cross blood brain barrier?	no information found; preliminary studies show intracranial activity in patients with brain metastases[4]
	volume of distribution	1670 L
	plasma protein binding	97.1%
Metabolism	primarily metabolized by CYP 2C8 and to a lesser extent via CYP 3A4	
	active metabolite(s)	ONT-993
	inactive metabolite(s)	no information found
Excretion	predominantly eliminated via hepatobiliary route	
	urine	4%
	feces	86%
	terminal half life	8.7 h
	clearance	148 L/h
Ethnicity	no clinically meaningful difference	

Adapted from standard reference[1-3] unless specified otherwise.

USES:

Primary uses:

*Breast cancer

Other uses:

*Health Canada approved indication

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SPECIAL PRECAUTIONS:

Caution:
- ***drug interactions*** involving the CYP 2C8 metabolism pathway are possible; tucatinib dose adjustment may be required[2,3]
- patients with pre-existing ***hepatic impairment*** may require starting dose reduction[2,3]

Special populations:
- patients ***aged 65 years and older*** may experience a higher incidence of grade 3 (or higher) diarrhea and vomiting and may be more likely to discontinue treatment due to adverse events[2,3]

Carcinogenicity: no information found

Mutagenicity: Not mutagenic in Ames test. Tucatinib is not clastogenic in mammalian *in vitro* and *in vivo* chromosome tests.[2,3]

Fertility: In animal studies, findings in female test subjects included decreased corpora lutea and corpus luteum cysts, increased ovarian interstitial cells, uterine atrophy, and mucification of the vagina at exposures approximately 0.05 times those seen following human clinical exposure. Male test subjects had atrophy/edema of the testes, oligospermia, and germ cell debris in the epididymides at exposures approximately 13 times higher than those seen following human clinical exposure.[2,3]

Pregnancy: In animal studies, tucatinib caused teratogenicity and embryo-fetal toxicity. Increased resorptions, reduced number of live fetuses, and skeletal, visceral, and external malformations were observed at exposures approximately equal to those seen following human clinical exposure. Pregnancy tests are recommended prior to starting treatment for female patients of childbearing potential. Effective contraception is recommended during treatment and for at least one week after the last dose in female patients of childbearing potential and in male patients with female partners of childbearing potential. Male patients should not donate or store semen during treatment and for at least one month after the last dose.[2,3]

Breastfeeding is not recommended due to the potential secretion into breast milk. Women should not breastfeed during treatment and for one week following the last dose.[2,3]

SIDE EFFECTS:

The table includes adverse events that presented during drug treatment but may not necessarily have a causal relationship with the drug. Because clinical trials are conducted under very specific conditions, the adverse event rates observed may not reflect the rates observed in clinical practice. Adverse events are generally included if they were reported in more than 1% of patients in the product monograph or pivotal trials, and/or determined to be clinically important[5,6]. When placebo-controlled trials are available, adverse events will generally be included if the incidence is ≥5% higher in the treatment group. **Incidence data in the Side Effect table is based solely on combination therapy with trastuzumab and capecitabine.**

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
blood and lymphatic system/ febrile neutropenia	***anemia*** (21-59%, severe 3-4%)
	neutropenia (<10%)
	thrombocytopenia (<10%)
cardiac	***cardiac failure*** (<1%)
	palpitations (2%)

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ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
gastrointestinal	*emetogenic potential:* moderate[7]
	diarrhea (81%, severe 13%); see paragraph following **Side Effects** table
	dysphagia (<10%)
	nausea (58%, severe 4%)
	rectal hemorrhage (1%)
	stomatitis (32%, severe 3%)
	vomiting (36%, severe 3%)
general disorders and administration site conditions	chest discomfort (<10%)
	influenza-like illness (<10%)
	non-cardiac chest pain (<10%)
	peripheral swelling (<10%)
	pyrexia (<10%)
hepatobiliary	***hepatotoxicity*** (42%, severe 9%); see paragraph following **Side Effects** table
infections and infestations	***septic shock*** (<1%)
investigations	alkaline phosphatase increase (26%, severe <1%)
	ALT increase (46%, severe 8%)
	AST increase (43%, severe 6%)
	bilirubin increase (47%, severe 2%)
	creatinine increase (14-33%); see paragraph following **Side Effects** table
	glomerular filtration rate decrease (<10%)
	magnesium decrease (40%, severe <1%)
	phosphate decrease (57%, severe 8%)
	potassium decrease (36%, severe 6%)
	sodium decrease (28%, severe 3%)
	weight decrease (13%, severe 1%)
metabolism and nutrition	appetite decrease (25%, severe <1%)
	dehydration (<10%)
	hyperglycemia (<10%)
	hypernatremia (<10%)
	hypoglycemia (<10%)
musculoskeletal and connective tissue	arthralgia (15%, severe <1%)
	musculoskeletal weakness (<10%)
nervous system	lethargy (<10%)
	peripheral neuropathy (13%, severe <1%)

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ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
	seizure (3%)
psychiatric	depression (4%)
renal and urinary	dysuria (<10%)
	urinary incontinence (<10%)
reproductive system and breast disorders	***vaginal hemorrhage*** (1%)
respiratory, thoracic and mediastinal	epistaxis (12%)
skin and subcutaneous tissue	***alopecia*** (5%)
	night sweats (<10%)
	palmar-plantar erythrodysesthesia syndrome (63%, severe 13%)
	rash (20%, severe <1%)
	skin ulcer (1%)
vascular	hypotension (<10%)

Adapted from standard reference[2,3,8] unless specified otherwise.

Increased serum creatinine occurs secondary to inhibition of renal tubular transport of creatinine via OCT2 and MATE1 transporters by tucatinib. Glomerular function is unaffected. Creatinine elevation usually occurs within the first 21 days of treatment, remains elevated but stable throughout treatment, and is reversible upon treatment discontinuation. Consider alternative markers to evaluate renal function during treatment, such as calculated GFR (if not based on creatinine), BUN, or cystatin C.[2]

Diarrhea is reported in up to 81% of patients. The majority of diarrhea events are grade 1 or 2, but severe diarrhea associated with dehydration, hypotension, acute kidney injury, and death has been reported. Median time to first episode is 12 days and 80% of events will resolve in about 8 days. Consider diagnostic tests to exclude infectious causes of severe diarrhea or diarrhea with complicating features (e.g., dehydration, fever, neutropenia). Use antidiarrheal treatment to manage diarrhea as clinically indicated. Based on the severity of the event, tucatinib treatment interruption, dose reduction, or treatment discontinuation may be required.[2,3]

Hepatotoxicity has been reported and can be severe. Median time to onset of ALT, AST, or bilirubin elevation is 36 days. The majority of events resolve by about 22 days. Based on the severity of the event, tucatinib treatment interruption, dose reduction, or treatment discontinuation may be required.[2,3]

INTERACTIONS:

AGENT	EFFECT	MECHANISM	MANAGEMENT
digoxin[1-3,9]	135% increase in C_{max} and 46% increase in AUC of digoxin	inhibition of P-gp by tucatinib	dose adjustment of digoxin may be required; monitor for digoxin-related toxicity
gemfibrozil[2,3]	62% increase in C_{max} and 204% increase in AUC of tucatinib	strong inhibition of CYP 2C8 by gemfibrozil	avoid concurrent use; if unavoidable, reduce tucatinib dose to 100 mg PO twice daily

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AGENT	EFFECT	MECHANISM	MANAGEMENT
itraconazole[2,3]	32% increase in C_{max} and 34% increase in AUC of tucatinib	strong inhibition of CYP 3A4 by itraconazole	not clinically significant; dose adjustment not usually required
metformin[2,3]	8% increase in C_{max} and 39% increase in AUC of metformin	inhibition of MATE1/MATE2-K mediated transport of metformin by tucatinib; tucatinib also reduces the renal clearance of metformin	clinical significance unknown; monitor blood glucose levels regularly
midazolam[2,3]	201% increase in C_{max} and 474% increase in AUC of midazolam	inhibition of CYP 3A4 by tucatinib	avoid concurrent use; if unavoidable, consider dose modification of midazolam and monitor for midazolam toxicity
omeprazole[2,3]	no clinically significant interaction	increased gastric pH by omeprazole; tucatinib solubility is not pH dependent	
repaglinide[2,3]	69% increase in C_{max} and 69% increase in AUC of repaglinide	inhibition of CYP 2C8 by tucatinib	dose modification of repaglinide may be required; monitor blood glucose levels regularly
rifampin[2,3]	37% decrease in C_{max} and 48% decrease in AUC of tucatinib	strong induction of CYP 3A4 and moderate induction of CYP 2C8 by rifampin	avoid concurrent use
tolbutamide[2,3]	no clinically significant interaction	inhibition of CYP 2C9 by tucatinib	

Tucatinib is a substrate of ***CYP 2C8***. CYP 2C8 ***inhibitors*** may increase the plasma concentration of tucatinib. Avoid concurrent use with *moderate* or *strong* CYP 2C8 inhibitors. If coadministration with *moderate* CYP 2C8 inhibitors cannot be avoided, monitor for tucatinib-related toxicity. If coadministration with *strong* CYP 2C8 inhibitors cannot be avoided, reduce tucatinib dose to 100 mg PO twice daily and increase monitoring for tucatinib-related toxicity. If the strong CYP 2C8 inhibitor is discontinued, tucatinib may be resumed at the prior dose following a washout period equal to 3 elimination half-lives of the inhibitor.
CYP 2C8 ***inducers*** may decrease the plasma concentration of tucatinib. Avoid concurrent use with *moderate* or *strong* CYP 2C8 inducers.[2,3]

Tucatinib is a substrate of ***CYP 3A4***. CYP 3A4 inducers may decrease the plasma concentration of tucatinib. Co-administration with strong CYP 3A4 *inhibitors* is not expected to result in a clinically significant interaction. Avoid concurrent use with strong CYP 3A4 *inducers*. [2,3]

Tucatinib is a reversible inhibitor of CYP 2C8 and a time-dependent inhibitor of CYP 3A4 *in vitro*. Avoid concurrent use with sensitive CYP 2C8 and CYP 3A4 substrates, such as those with narrow therapeutic index. If coadministration cannot be avoided, monitor for toxicity of the substrate; dose modification of the substrate may be required.[2,3]

Tucatinib is a substrate and inhibitor of P-glycoprotein (P-pg) *in vitro*. If coadministered with a P-gp substrate of narrow therapeutic index, monitor for toxicity of the substrate; dose modification of the substrate may be required.[2,3,9]

Tucatinib is a substrate of BCRP in vitro; clinical significance is unknown.[2,3]

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SUPPLY AND STORAGE:

Oral: Seagen Canada Inc. supplies tucatinib as 50 mg and 150 mg film-coated tablets. Store at room temperature.[2]

Additional information: Tucatinib 50 mg is supplied in bottles of 60 tablets. Tucatinib 150 mg is suppled in bottles of 60 or 120 tablets. Dispense tucatinib in original bottle with desiccant. Once the bottle is opened, discard remaining tablets after 3 months.[2]

DOSAGE GUIDELINES:

Refer to protocol by which patient is being treated. Numerous dosing schedules exist and depend on disease, response, and concomitant therapy.

Adults:

	BC Cancer usual dose noted in ***bold, italics***
Oral:[2,3,10,11]	***300 mg (range 150-300 mg) PO twice daily**** Administer with food or on an empty stomach, approximately 12 hours apart, at about the same time every day. *dose adjustment may be required for some drug interactions
Concurrent radiation:	no information found
Dosage in myelosuppression:	modify according to protocol by which patient is being treated
Dosage in renal failure: [2,3]	CrCl ≥30 mL/min: no starting dose adjustment required CrCl <30 mL/min: no information found calculated creatinine clearance = $\frac{N^* \times (140 - Age) \times \text{weight in kg}}{\text{serum creatinine in micromol/L}}$ * For males N=1.23; for females N=1.04
Dosage in hepatic failure:[2,3]	mild/moderate impairment (Child-Pugh A/B): no starting dose adjustment required severe impairment (Child-Pugh C): reduce starting dose to 200 mg PO twice daily
Dosage in dialysis:	no information found

Children: safety and efficacy have not been established[2]

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