DRUG NAME: Fruquintinib

SYNONYM(S): HMPL-013[1]

COMMON TRADE NAME(S): FRUZAQLA®

CLASSIFICATION: molecular targeted therapy

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

MECHANISM OF ACTION:

Fruquintinib is an orally administered tyrosine kinase inhibitor that selectively targets vascular endothelial growth factor receptors (VEGFR-1, VEGFR-2, VEGFR-3). VEGFRs are key regulators of angiogenesis, tumour growth and metastasis. Inhibition of VEGFR signaling reduces cell proliferation and tumour growth.[1,2]

PHARMACOKINETICS:

Oral Absorption	T_{max} = 2 h; time to steady state = 14 days; administration with a high fat meal had no clinically meaningful effect on fruquintinib pharmacokinetics compared to fasting	
Distribution	mainly bound to human serum albumin[3]	
	cross blood brain barrier?	no information found
	volume of distribution	48.5 L
	plasma protein binding	95%
Metabolism	primary metabolized by CYP 3A, with minor contribution from CYP 2C8, CYP 2C9, and CYP 2C19; also oxidized by sulfation and glucuronidation	
	active metabolite(s)	no information found
	inactive metabolite(s)	no information found
Excretion	primarily eliminated by renal elimination	
	urine	60% (0.5% unchanged)
	feces	30% (5% unchanged)
	terminal half life	42 h
	clearance	14.8 mL/min
Sex	no clinically significant differences in the pharmacokinetics of fruquintinib	
Elderly	no clinically significant differences in the pharmacokinetics of fruquintinib	
Ethnicity	no clinically significant differences in the pharmacokinetics of fruquintinib	

Adapted from standard reference[2] unless specified otherwise.

USES:

Primary uses:

*Colorectal cancer

Other uses:

*Health Canada approved indication

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SPECIAL PRECAUTIONS:

Caution:
- pre-existing ***hypertension*** should be adequately controlled prior to starting treatment[2]
- ***impaired wound healing*** is associated with VEGF inhibitors; consider holding fruquintinib for at least 2 weeks before and after surgery, and resume only after adequate wound healing[2]
- fatal ***gastrointestinal perforation*** has been reported with fruquintinib and other VEGF inhibitors; possible risk factors include recent history of endoscopy or prior abdominal surgeries or radiotherapy[4-6]
- fruquintinib is not recommended in patients with a ***thromboembolic event*** in the past 6 months or a history of stroke or transient ischemic attack in the past 12 months[2]

Carcinogenicity: Carcinogenicity studies have not been conducted.[2]

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

Fertility: In animal studies, decreased male and female reproductive indices were observed at exposures approximately 3- and 0.8-fold those expected with human clinical doses, respectively. The number of resorptions and pre- and post-implantation losses were increased, and the number of viable fetuses were reduced.[2,3,7]

Pregnancy: In animal studies, fruquintinib caused embryo lethality and teratogenic effects. External, visceral and skeletal anomalies were observed at exposures less than those expected with human clinical doses. Malformations affected the head, tail, tongue, blood vessels, heart, thymus, and skeleton (e.g., vertebrae, forelimb metacarpals and/or phalanges). Post-implantation losses were increased and the number of viable fetuses were reduced at subclinical exposure levels. Contraception is recommended during treatment and for at least 2 weeks after the last dose for female patients of childbearing potential and male patients with female partners of childbearing potential.[2,7]

Breastfeeding is not recommended due to the potential secretion into breast milk. Women should not breastfeed during treatment and for 2 weeks after the last dose of fruquintinib.[2]

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.[8,9] When placebo-controlled trials are available, adverse events will generally be included if the incidence is ≥5% higher in the treatment group.

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
blood and lymphatic system/ febrile neutropenia	leukopenia (10-14%, severe <1%)
	neutropenia (7-11%, severe <1%)
	thrombocytopenia (10-25%, severe 1-4%)
endocrine	hypothyroidism (24-37%, severe <1%); median time to onset is 56 days[3]
gastrointestinal	*emetogenic potential:* minimal (rare)[10]
	diarrhea (13-20%, severe 3-4%)
	gastrointestinal perforation/fistula (1-2%, severe 1%)[11]; fatalities reported

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ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
	gastrointestinal hemorrhage (7%, severe 1%); see paragraph following **Side Effects** table
	pancreatitis (<1%)
	stomatitis (11-23%, severe 1-2%)
general disorders and administration site conditions	asthenia/fatigue (11%, severe 4%)
hepatobiliary	***hepatic failure***/encephalopathy (severe <1%)[7]; see paragraph following **Side Effects** table
infections and infestations	***infections*** (10%, severe 6%)[3]
	pneumonia (3%, severe <1%)
	upper respiratory tract infection (3%)
	urinary tract infection (7%)
injury, poisoning, and procedural complications	***impaired wound healing*** (<1%)
investigations	***ALT increase*** (6-15%, severe 3%)
	AST increase (6-12%, severe 1-2%)
	blood bilirubin increase (5-12%)
	cholesterol increase (15%)
	creatinine increased (12%)
	serum amylase increase (9%, severe 3%)
	triglycerides increase (31%, severe 2%)
metabolism and nutrition	anorexia, including decreased appetite and weight loss (9-18%, severe 1-3%)
	hyperglycemia (12%, severe 1%)
	hypermagnesemia (9%, severe 2%)
	hypernatremia (8%)
	hypokalemia (7-12%, severe 3%)
	hypomagnesemia (6-10%)
musculoskeletal and connective tissue	arthralgia (7-11%, severe <1%)
	musculoskeletal pain/discomfort (10%, severe <1%)
nervous system	***posterior reversible encephalopathy syndrome*** (<1%); see paragraph following **Side Effects** table
renal and urinary	***proteinuria*** (13-25%, severe 5%); see paragraph following **Side Effects** table
respiratory, thoracic, and mediastinal	dysphonia (13-36%)
	epistaxis (7%)
	throat pain (8%)
skin and subcutaneous tissue	***hand-foot skin reaction*** (16-46%, severe 6-11%); median time to onset is 19 days

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ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
vascular	artery dissection/aneurysm
	arterial thromboembolic events (1%); see paragraph following **Side Effects** table
	hemorrhage (12%, severe 2%)[3]; see paragraph following **Side Effects** table
	hypertension (30-44%, severe 13-21%); see paragraph following **Side Effects** table

Adapted from standard reference[2,7] unless specified otherwise.

Hypertension usually occurs in the first cycle of treatment. Median time to onset is 14 days (range: 1 day to 7 months). Pre-existing hypertension should be adequately controlled prior to starting fruquintinib. Monitor blood pressure frequently during the first month of therapy and regularly thereafter as indicated. Management of hypertension may include initiation or modification of antihypertensive therapy and/or fruquintinib dose interruption or dose reduction. Permanently discontinue fruquintinib for hypertensive crisis or uncontrolled hypertension despite antihypertensive therapy.[2,7]

Hemorrhagic events, including fatal cases of gastrointestinal bleeding, have been reported. Median time to onset is 22 days (range: 1 day to 10 months). In patients treated with anticoagulants, more frequent monitoring of INR is recommended. Fruquintinib dose interruption and/or dose reduction may be required. Permanently discontinue fruquintinib for severe or life-threatening hemorrhage.[2,7]

Hepatotoxicity has been reported with fruquintinib, including fatal cases of hepatic failure and encephalopathy.[7] Median time to onset of elevated liver enzymes is 27 days (range: 4 days to 12 months). Based on the severity and persistence of hepatotoxicity, treatment interruption and/or dose reduction may be required.[2]

Posterior reversible encephalopathy syndrome (PRES), a rare neurologic disorder, has been reported with fruquintinib. Symptoms may include seizure, headache, altered mental status, visual or neurological disturbances, or blindness, with or without associated hypertension. Brain imaging is necessary to confirm diagnosis. Permanently discontinue fruquintinib in patients who develop PRES.[2]

Proteinuria is associated with anti-VEGF therapy and is reported with fruquintinib. Median time to onset is 28 days (range: 6 days to 1 year). Dipstick urinalysis is recommended for monitoring throughout treatment. If proteinuria greater than or equal to 2 grams per 24 hours occurs, fruquintinib dose interruption, dose reduction, or discontinuation may be necessary. Permanently discontinue fruquintinib for nephrotic syndrome.[2]

Thromboembolic events have been reported with fruquintinib. Fruquintinib is not recommended in patients with a history of thromboembolic events (including deep vein thrombosis and pulmonary embolism) in the past 6 months or a history of stroke or transient ischemic attack within the last 12 months. Immediately discontinue fruquintinib if arterial thrombosis is suspected.[2]

INTERACTIONS:

AGENT	EFFECT	MECHANISM	MANAGEMENT
dabigatran etexilate[2]	no clinically meaningful changes in dabigatran AUC	inhibition of P-gp by fruquintinib	no dose adjustment of dabigatran is required
dexamethasone[2]	*predicted*: no clinically meaningful changes in fruquintinib AUC	weak induction of CYP 3A4 by dexamethasone	no dose adjustment of fruquintinib is required

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AGENT	EFFECT	MECHANISM	MANAGEMENT
efavirenz[2]	*predicted*: 32% decrease in fruquintinib AUC and 4% decrease in C_{max}	moderate induction of CYP 3A4 by efavirenz	if concurrent use is unavoidable, fruquintinib may be continued without dose adjustment
itraconazole[2]	no clinically meaningful changes in fruquintinib AUC and C_{max}	strong inhibition of CYP 3A4 by itraconazole	no dose adjustment of fruquintinib is required
rabeprazole[2]	no clinically meaningful changes in fruquintinib AUC	pH-dependent solubility of fruquintinib	no dose adjustment of fruquintinib is required during concurrent use of gastric acid lowering agents
rifampin[2]	65% decrease in fruquintinib AUC and 12% decrease in C_{max}	strong induction of CYP 3A4 by rifampin	avoid concurrent use
rosuvastatin[2]	no clinically meaningful changes in rosuvastatin AUC	inhibition of BCRP by fruquintinib	no dose adjustment of rosuvastatin is required

Fruquintinib is a *substrate* of CYP 3A4. Strong or moderate ***CYP 3A4 inducers*** may decrease the plasma concentration of fruquintinib; avoid concurrent use if possible. Coadministration of fruquintinib with an index ***CYP 3A4 inhibitor*** did not result in clinically significant changes in the pharmacokinetics of fruquintinib; therefore, no dose adjustment of fruquintinib is required during coadministration with CYP 3A4 inhibitors.[2]

In vitro, fruquintinib inhibits P-gp and BCRP; however, no clinically meaningful interactions have been reported. [2]

SUPPLY AND STORAGE:

Oral: Takeda Canada Inc. supplies fruquintinib as 1 mg and 5 mg capsules. The 1 mg capsule shell contains tartrazine.[7] Store at room temperature.[2]

DOSAGE GUIDELINES:

Refer to protocol by which patient is being treated.

Adults:

BC Cancer usual dose noted in ***bold, italics***

	Cycle Length:	
Oral[2,12,13]*:*	4 weeks:	***5 mg*** (range 3-5 mg) ***PO once daily for 21 consecutive days***, starting on day 1 (total dose per cycle 105 mg [range 63-105 mg]) Administer with food or on an empty stomach, approximately the same time each day
Concurrent radiation:	no information found	

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Dosage in renal failure:	mild to severe impairment (CrCL ≥15 mL/min): no adjustment required[2,3]
	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:	mild to moderate impairment (total bilirubin ≤3 x ULN): no adjustment required[2,3] severe impairment (total bilirubin >3 x ULN): no information found
Dosage in dialysis:	no information found

Children: safety and efficacy have not been established

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