DRUG NAME: Gilteritinib

SYNONYM(S): ASP2215[1]

COMMON TRADE NAME(S): XOSPATA®

CLASSIFICATION: molecular targeted therapy

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

MECHANISM OF ACTION:

Gilteritinib is a small molecule, multi-targeted oral tyrosine kinase inhibitor. It inhibits receptor signaling and proliferation in cells that express FMS-like tyrosine kinase 3 (FLT3), including FLT3-internal tandem duplication (ITD), tyrosine kinase domain mutations (TKD) FLT3-D835Y and FLT3-ITD-D835Y. Gilteritinib also induces apoptosis in cancer cells expressing FLT3-ITD.[1-3]

PHARMACOKINETICS:

Oral Absorption	T_{max}: 4-6 h (fasted state) food effect: high-fat, high-calorie food intake reduces C_{max} by 26% and delays T_{max} by 2 h	
Distribution	extensive tissue distribution	
	cross blood brain barrier?	no information found
	volume of distribution	central: 1092 L; peripheral: 1100 L
	plasma protein binding	90% (primarily serum albumin)
Metabolism	primarily by CYP 3A4	
	active metabolite(s)	M17 (via N-dealkylation and oxidation), M16 and M10 (via N-dealkylation)
	inactive metabolite(s)	no information found
Excretion	mainly fecal elimination	
	urine	16.4%
	feces	64.5%
	terminal half life	113 h
	clearance	14.85 L/h

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

USES:

Primary uses:

*Leukemia, acute myeloid

Other uses:

*Health Canada approved indication

SPECIAL PRECAUTIONS:

Caution:

- ***QT interval prolongation*** has been reported; monitor ECG and electrolytes in patients with known risk factors and correct hypokalemia and/or hypomagnesemia prior to treatment[2,3]

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Carcinogenicity: no information found

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

Fertility: In animal studies, gilteritinib administration was associated with degeneration and necrosis of germ cells, spermatid giant cell formation in the testis, and single cell necrosis of the epididymal duct epithelia at lower exposures than those seen following human clinical exposure.[2,3]

Pregnancy: In animal studies, gilteritinib and/or its metabolites were shown to pass through the blood-placental barrier, transferring to the fetus. Gilteritinib was teratogenic when administered during organogenesis at lower maternal exposures than those seen following human clinical exposure. Reported findings included embryo-fetal death, decreased fetal body and placental weight, and increased external, visceral, and skeletal abnormalities. Female patients of childbearing potential should use effective contraception during treatment and for at least six months after the last dose. Male patients with female partners of reproductive potential should use effective contraception for at least four months after the last dose.[2,3]

Breastfeeding is not recommended due to the potential secretion into breast milk. In animal studies, gilteritinib and/or its metabolites were distributed to infant tissues through milk. Women should wait two months after the last dose before breastfeeding.[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[4].

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
blood and lymphatic system/ febrile neutropenia	anemia (16-23%, severe 3%)[5]
	febrile neutropenia (6-9%)[6]
	neutropenia (7-9%, severe 1%)[5]
	thrombocytopenia (10-14%, severe 1-2%)[5]
cardiac	***cardiac failure*** (1-4%); fatal events reported
	myocarditis (1%)
	pericardial effusion (4%)
	pericarditis (2%)
eye	eye disorders (25%); see paragraph following **Side Effects** table
gastrointestinal	*emetogenic potential:* low[7]
	abdominal pain (11-18%, severe 2%)
	constipation (13-31%, severe 1%)
	diarrhea (12-35%, severe 4-5%)
	large intestine perforation (severe 1%); fatal events reported[8]
	nausea (10-32%, severe 2%)

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ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
	pancreatitis (1-5%); fatal events reported
	stomatitis (12-41%, severe 1-7%)
	vomiting (21-22%, severe <1%)
general disorders and administration site conditions	asthenia (15%, severe 2%)
	fatigue/malaise (24-44%, severe 1-6%)
	fever (11-41%, severe 1-13%)
	peripheral edema (13-40%, severe <1%)
immune system	anaphylactic reaction (1-8%)
infections and infestations	***pneumonia*** (severe 1%); fatal events reported[8]
	septic shock (severe 1%); fatal events reported[8]
investigations	alkaline phosphatase increase (21%)
	ALT increase (31-38%, severe 4-10%)
	AST increase (31-38%, severe 3-10%)
	QTc prolongation (7-9%)
metabolism and nutrition	appetite decrease (15-18%, severe 2%)
musculoskeletal and connective tissue	arthralgia/myalgia (11-50%, severe 1-7%)
	muscular weakness (9%)
	musculoskeletal pain (4%)
	myositis (2%)
	pain in extremity (15%, severe 1%)
nervous system	dizziness (11-22%, severe <1%)
	dysgeusia (10-11%)
	headache (11-26%, severe 1%)
	peripheral neuropathy (5-18%)
	posterior reversible encephalopathy syndrome (1%); see paragraph following **Side Effects** table
	syncope (5%, severe 3%)
psychiatric	insomnia (15%)
renal and urinary	***acute kidney injury*** (severe 7-8%)
	renal impairment (21%)
respiratory, thoracic and mediastinal	cough (12-29%, severe <1%)
	differentiation syndrome (3%, severe 2%); see paragraph following **Side Effects** table
	dyspnea (11-35%, severe 1-12%)
skin and subcutaneous	acute febrile neutrophilic dermatosis (3%)

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ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
tissue	rash (10-36%, severe <1%)
vascular	***hypotension*** (17-22%, severe 3-8%)

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

Differentiation syndrome is a group of symptoms associated with rapid proliferation and differentiation of myeloid cells. It is uncommon but can be life-threatening or fatal if not treated. Time to onset can be as early as 1 day and up to 82 days after treatment initiation. It may present with or without concomitant leukocytosis. Monitor for symptoms and clinical findings such as fever, dyspnea, rapid weight gain, hypotension, rash, pleural or pericardial effusion, pulmonary or peripheral edema, and renal dysfunction. Patients may have concomitant acute febrile neutrophilic dermatosis. Initiate corticosteroid therapy and hemodynamic monitoring if differentiation syndrome is suspected and continue until symptom resolution. After resolution of symptoms, taper corticosteroids to prevent symptom recurrence due to premature discontinuation. Gilteritinib treatment interruption is recommended if severe signs or symptoms persist for more than 48 hours after corticosteroid initiation.[2,3]

A variety of ***eye disorders*** have been reported including dry eye, blurred vision, eye pain, conjunctival edema, retinal or conjunctival hemorrhage, blepharitis, cataract, retinopathy, and vitreous detachment. Monitor patients for symptoms or changes in eyesight.[9]

Posterior reversible encephalopathy syndrome (PRES) has been reported with symptoms including seizure and altered mental status. Confirm diagnosis with brain imaging and discontinue gilteritinib in patients who develop PRES.[2,3]

INTERACTIONS:

AGENT	EFFECT	MECHANISM	MANAGEMENT
fluconazole[2,3]	16% increase in C_{max} and 40% increase in AUC of gilteritinib	moderate inhibition of CYP 3A4 by fluconazole	not considered clinically significant; dose adjustment not required
itraconazole[2,3]	20% increase in C_{max} and 120% increase in AUC of gilteritinib	strong inhibition of CYP 3A4 and P-glycoprotein by itraconazole	consider alternative therapy; if concomitant use unavoidable, monitor for gilteritinib-related toxicity
rifampin[2,3]	30% decrease in C_{max} and 70% decrease in AUC of gilteritinib	strong induction of CYP 3A4 and P-glycoprotein by rifampin	avoid concurrent use

Gilteritinib is a ***substrate*** of ***CYP 3A4*** and ***P-glycoprotein (P-gp)***. Concomitant use with strong ***inducers*** of CYP 3A4 and/or P-gp should be avoided as they may decrease gilteritinib exposure and compromise treatment efficacy. Concomitant use with strong ***inhibitors*** of CYP 3A4 and/or P-gp may increase gilteritinib exposure. Consider alternative therapies where possible; if concomitant use cannot be avoided, monitor for gilteritinib-related toxicity. Grapefruit and grapefruit juice may inhibit CYP 3A4 metabolism of gilteritinib in the intestinal wall and theoretically may increase gilteritinib plasma levels; clinical significance is unknown.[2,3]

In vitro, gilteritinib may reduce the effects of drugs that target $5HT_{2B}$ or sigma nonspecific receptors and may inhibit organic cation transporter (OCT)1 and breast cancer resistance protein (BCRP); clinical significance is unknown.[2,3]

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SUPPLY AND STORAGE:

Oral: Astellas Pharma Canada, Inc. supplies gilteritinib as 40 mg film-coated tablets. Store at room temperature.[2]

DOSAGE GUIDELINES:

Refer to protocol by which patient is being treated. Numerous dosing schedules exist and depend on disease, response, and concomitant therapy. Guidelines for dosing also include consideration of absolute neutrophil count (ANC). Dosage may be reduced, delayed or discontinued in patients with bone marrow depression due to cytotoxic/radiation therapy or with other toxicities.

Adults:

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

Oral:[2,3,10]

120 mg (range 80 – 120 mg) ***PO once daily***

Administer with food or on an empty stomach.

In the absence of clinical response, an increase to 200 mg PO once daily may be considered[2,8,10]; refer to protocol by which patient is being treated.

Patients proceeding to hematopoietic stem cell transplantation (HSCT) should stop gilteritinib one week before HSCT conditioning regimen.

Concurrent radiation: no information found

Dosage in myelosuppression: modify according to protocol by which patient is being treated

Dosage in renal failure:

CrCl ≥30 mL/min: no adjustment required[2,3]
CrCl <30 mL/min: no information found

$$\text{calculated creatinine clearance} = \frac{N^* \times (140 - \text{Age}) \times \text{weight in kg}}{\text{serum creatinine in micromol/L}}$$

* For males N=1.23; for females N=1.04

Dosage in hepatic failure:

mild or moderate impairment (Child-Pugh A or B): no adjustment required[2,3]
severe impairment (Child-Pugh C): no information found

Dosage in dialysis: no information found

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

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