Drug Monograph

A - Drug Name

gilteritinib

COMMON TRADE NAME(S): Xospata®

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B - Mechanism of Action and Pharmacokinetics

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

Absorption	Peak plasma levels	~ 4-6 hours (fasted state)
	Effects with food	The Cmax was decreased by 26% with the co-ingestion of a high-fat meal with a tmax delay of 2 hours.
	Time to reach steady state	15 days
Distribution	In general, gilteritinib exhibits linear, dose-proportional pharmacokinetics in patients with relapsed or refractory acute myeloid leukemia (AML).	
	PPB	~ 90% (primarily serum albumin)
Metabolism	Gilteritinib is primarily metabolised via CYP3A4	
	Active metabolites	Yes

Elimination	Feces	65%
	Urine	16%
	Half-life	113 hours

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C - Indications and Status

Health Canada Approvals:

- Acute Myeloid Leukemia (AML)

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

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D - Adverse Effects

Emetogenic Potential: Low – No routine prophylaxis; PRN recommended

The following table lists adverse effects that occurred in ≥ 10% of patients in a phase III study for adult patients with relapsed or refractory AML having a FLT3 mutation, comparing gilteritinib with salvage chemotherapies. Side effects marked with a "†" are from a comparison with a pre-selected low intensity chemotherapy subgroup. The table also includes severe and life-threatening adverse effects from post-marketing or other sources.

ORGAN SITE	SIDE EFFECT* (%)	ONSET**
Cardiovascular	Cardiotoxicity (1%)	E
	Hypotension (18%)	E
	Pericardial effusion (4%)	E
	Pericarditis (2%) (including myocarditis)	E
	QT interval prolonged (9%) (3% severe)	E
Dermatological	Rash (15%)	E
Gastrointestinal	Abdominal pain (15%)	E
	Anorexia (18%)	E

	Constipation (31%)	E
	Diarrhea (33%)	E
	Mucositis (14%)	E
	Nausea, vomiting (32%)	E
General	Edema - limbs (24%)	E
	Fatigue (29%)	E
Hematological	Febrile neutropenia (27%) †	E
	Other - differentiation syndrome (3%) (may be severe)	E
Hepatobiliary	↑ LFTs (36%) †	E
	Pancreatitis (<1%)	E
Hypersensitivity	Anaphylaxis (1%)	I E
Metabolic / Endocrine	Other - creatine kinase (7% severe)	E
Musculoskeletal	Musculoskeletal pain (15%)	E
Nervous System	Dizziness (20%)	E
	Dysgeusia (10%)	E
	Headache (26%)	E
	Myositis (2%)	E
	Peripheral neuropathy (5%)	E
	Posterior reversible encephalopathy syndrome (PRES) (<1%)	E
Ophthalmic	Eye disorders (25%)	E
Renal	Other (7%) - Acute kidney injury	E
Respiratory	Cough, dyspnea (29%)	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 gilteritinib include ↑ LFTs, diarrhea, nausea, vomiting, constipation, cough, dyspnea, fatigue, febrile neutropenia, headache, eye disorders and peripheral edema.

Prolonged **cardiac ventricular repolarization** (QT interval), QTc interval >500 msec and increases from baseline >60 msec have been reported with gilteritinib. Fatal cases of cardiac failure have also been reported.

Uncommon events of **posterior reversible encephalopathy syndrome** (PRES) have been reported with symptoms including seizure and altered mental status. Symptoms have resolved after discontinuation of gilteritinib.

Symptoms of **differentiation syndrome** (rapid proliferation and differentiation of myeloid cells), which can be fatal or life-threatening if not treated has been reported with gilteritinib. Symptoms may include fever, dyspnea, pleural effusion, pericardial effusion, pulmonary edema, hypotension, rapid weight gain, peripheral edema, rash, and renal dysfunction. Some cases had concomitant acute febrile neutrophilic dermatosis. The onset of differentiation syndrome (with or without concomitant leukocytosis) ranged from 1 to 82 days after gilteritinib initiation; the majority of patients who experienced this syndrome recovered after treatment or therapy interruption.

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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.

A validated test is required to confirm the FLT3 mutation prior to initiation of treatment.

Correct hypokalemia or hypomagnesemia prior to gilteritinib administration.

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

- Gilteritinib treatment may be restarted ≥ 30days after the transplantation if engraftment is successful and patient is in CRc* and has no grade ≥ 2 acute graft versus host disease or uncontrolled complications of transplantation.

*composite complete remission (CRc) is defined as the remission rate of all CR, CRp (achieved CR except for incomplete platelet recovery (<100 x 10^9/L)), and CRi (achieved CR except for incomplete hematological recovery with residual neutropenia (< 1 x 10^9/L) +/- complete platelet recovery).

Adults:

Oral: 120* mg Once daily

* Dose escalation up to 200 mg daily in the absence of clinical response may be considered

Dosage with Toxicity:

Dose Levels

Dose Level	Gilteritinib Dose (mg/day)
0	120
-1	80

Toxicity	Grade	Action
Symptoms of Differentiation Syndrome	Any	If suspected, administer corticosteroids* for a minimum of 3 days and initiate hemodynamic monitoring until symptom resolution. Taper corticosteroids after resolution of symptoms. Hold if severe signs and/or symptoms persist for > 48 hours after corticosteroid initiation. With resolution to ≤ grade 2, restart at the same dose level .
Symptoms of Posterior Reversible Encephalopathy Syndrome (PRES)	Any	Discontinue
QTc interval	>500 msec	Hold until QTc interval is within 30 msec of baseline or ≤480 msec. Restart at 1 dose level ↓.
	Increased by >30 msec on ECG on day 8 of cycle 1	Confirm with a repeat ECG on day 9. If confirmed, consider ↓ by 1 dose level .
Pancreatitis	Any	Hold until resolved. Restart at 1 dose level ↓.
Other toxicity (considered related to treatment)	≥ Grade 3	Hold until resolved to grade 1. Restart at 1 dose level ↓.

*dexamethasone 10 mg IV every 12 hours (or an equivalent dose of an alternative oral or IV corticosteroid)

Dosage with Hepatic Impairment:

Mild or moderate hepatic impairment had no clinically meaningful effects on gilteritinib pharmacokinetics.

Hepatic Impairment	Gilteritinib Starting Dose
Mild (Child Pugh A)	No dose adjustment required.
Moderate (Child Pugh B)	
Severe (Child Pugh C)	No data available

Dosage with Renal Impairment:

Mild or moderate renal impairment had no clinically meaningful effects on gilteritinib pharmacokinetics.

It is not known if gilteritinib is removed by dialysis.

CrCl (mL/min)	Gilteritinib Dose
≥ 30	No adjustment required
< 30	Limited data available

Dosage in the elderly:

No dose adjustment required; no overall differences in efficacy or safety were observed in patients ≥ 65 years of age compared to younger patients.

Dosage based on gender:

Gender has no significant effect on the pharmacokinetics of gilteritinib.

Dosage based on ethnicity:

Race has no significant effect on the pharmacokinetics of gilteritinib.

Children:

Safety and efficacy in children have not been established.

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F - Administration Guidelines

- Administer tablets orally with or without food, about the same time each day.
- Do not break or crush tablets.
- Grapefruit, starfruit, Seville oranges, their juices or products should be avoided during gilteritinib treatment.
- If a dose is missed, administer the missed dose as soon as possible on the same day if there is ≥12 hours until the next scheduled dose (do not administer 2 doses within 12 hours). Return to the normal dosing schedule the following day.
- If vomiting occurs after dosing, patients should not take another dose, but should return to the normal schedule the following day.
- Store at room temperature 15ºC to 30ºC.
- Keep container tightly closed, and protect from light, moisture and humidity.

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G - Special Precautions

Contraindications:

- Patients who have a hypersensitivity to this drug or any of its components

Other Warnings/Precautions:

- Use with caution in patients with acute promyelocytic leukemia (APL) or AML related to previous chemotherapy or radiation as they were excluded from clinical trials.

- Dizziness and syncope have been reported in patients taking gilteritinib; caution is required when driving or operating machinery.

Other Drug Properties:

- Phototoxicity: No
- Carcinogenicity: Unknown

Pregnancy and Lactation:

- Mutagenicity: No
- Teratogenicity: Yes
- Embryotoxicity: Yes
  Gilteritinib is not recommended for use in pregnancy. Adequate contraception should be used by both sexes during treatment, and for at least **6 months** after the last dose in women and at least **4 months** after the last dose in men.
- Breastfeeding:
  Breastfeeding is not recommended during treatment and for at least **2 months** after the last dose.
- Fertility effects: Documented in animals
  Gilteritinib may impair fertility in male patients of reproductive potential.

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H - Interactions

Gilteritinib is primarily metabolised by CYP3A enzymes but is not an inducer of CYP3A. Gilteritinib is a substrate of P-glycoprotein (P-gp) and can inhibit organic cation transporter (OCT)1 and breast cancer resistance protein (BCRP).

AGENT	EFFECT	MECHANISM	MANAGEMENT
CYP3A4 inducers (i.e. phenytoin, rifampin, dexamethasone, carbamazepine, phenobarbital, St. John's Wort, etc)	↓ gilteritinib concentration and/or efficacy. Concomitant use with rifampin (a combined P-gp and strong CYP3A inducer) reduced gilteritinib Cmax by 30% and AUC by 70%.	↑ metabolism of gilteritinib	Avoid concomitant use with strong CYP3A4 inducers.
P-gp inducers (i.e. dexamethasone, rifampin)	↓ gilteritinib concentration and/or efficacy	↑ metabolism of gilteritinib	Avoid concomitant use with P-gp inducers.

CYP3A4 inhibitors (i.e. ketoconazole, clarithromycin, ritonavir, fruit or juice from grapefruit, Seville oranges or starfruit)	↑ gilteritinib concentration and/or toxicity. Concomitant use with itraconazole (a combined P-gp and strong CYP3A inhibitor) increased gilteritinib Cmax by 20% and AUC by 120%.	↓ metabolism of gilteritinib	Consider alternative therapies to strong CYP3A4 inhibitors. If concomitant use cannot be avoided, monitor closely for gilteritinib-related toxicity.
P-gp inhibitors (i.e. quinidine, verapamil, cyclosporine)	↑ gilteritinib concentration and/or toxicity	↓ metabolism of gilteritinib	Consider alternative therapies to strong P-gp inhibitors. If concomitant use cannot be avoided, monitor closely for gilteritinib-related toxicity.
5HT2B receptor or sigma nonspecific receptor substrates (e.g., escitalopram, fluoxetine, sertraline)	↓ substrate concentration and/or efficacy	Gilteritinib inhibits substrate binding to the 5HT2B and sigma receptors	Avoid concomitant use unless use is considered essential.
Substrates of P-gp (e.g. digoxin, dabigatran etexilate), BCRP (e.g. mitoxantrone, rosuvastatin), and OCT1 (metformin)	↑ substrate concentration and/or toxicity	Gilteritinib inhibits these transporters in vitro	Caution, monitor especially for substrates with narrow therapeutic range. Substrate dose modification may be required.

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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, at least once weekly for the first month, once every other week for the second month, and once monthly for the duration of treatment
Blood chemistry (including creatine kinase, creatinine, electrolytes)	Baseline, at least once weekly for the first month, once every other week for the second month, and once monthly for the duration of treatment
ECG	Baseline, on days 8 and 15 of cycle 1 and prior to the start of the next 2 months of treatment and then as clinically indicated
Clinical toxicity assessment for differentiation syndrome, infection, pancreatitis, hypersensitivity reactions and cardiovascular, gastrointestinal, neurologic and ophthalmic effects	As clinically indicated

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

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J - Supplementary Public Funding

Exceptional Access Program (EAP Website)

- gilteritinib - Relapsed or refractory FLT3-mutated Acute Myeloid Leukemia

High Cost Therapy Funding Program

- Gilteritinib (Inpatient) - Relapsed or Refractory FLT3-mutated Acute Myeloid Leukemia

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K - References

Perl AE, Martinelli G, Cortes JE, et al. Gilteritinib or chemotherapy for relapsed or refractory FLT3-mutated AML. N Engl J Med 2019;381(18):1728-1740.

Prescribing Information: Xospata® (gilteritinib). Astellas Pharma Canada, Inc. January 2022.

Product Monograph: Xospata® (gilteritinib). Astellas Pharma US, Inc., May 2019 and Jan 2022.

Summary of Product Characteristics: Xospata (gilteritinib). Astellas Pharma Ltd, Surrey, UK., July 2021.

July 2023 Modified Drug interactions section

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L - Disclaimer

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

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