XOSPATA™
Prescribing Guide

Therapeutic Indications

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Therapeutic Indications

Indicated as monotherapy
for the treatment of adult patients who have relapsed or refractory acute myeloid leukaemia (AML) with a FLT3 mutation

Before taking gilteritinib,
relapsed or refractory AML patients must have confirmation of FMS-like tyrosine kinase 3 (FLT3) mutation (internal tandem duplication [ITD] or tyrosine kinase domain [TKD]) using a validated test.

Xospata may be re-initiated
in patients following haematopoietic stem cell transplantation (HSCT)

Posology

Recommended starting dose - 120 mg
(three 40 mg tablets) once daily.

Blood chemistries, including creatine phosphokinase
Prior to initiation of treatment, on day 15 and monthly for the duration of treatment.

Electrocardiogram (ECG)
Before initiation of treatment, on day 8 and 15 of cycle 1 and prior to the start of next three subsequent months of treatment.

Treatment
Continue until the patient is no longer clinically benefiting or until unacceptable toxicity.

Response may be delayed
Continuation for treatment at the prescribed dose for up to 6 months should be considered to allow time for a clinical response.

In the absence of a response [patient did not achieve a composite complete remission (CRc)] after 4 weeks of treatment
Dose can be increased to 200 mg (five 40 mg tablets) once daily, if tolerated or clinically warranted.

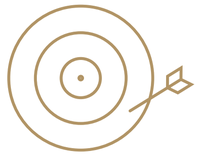
Xospata dose interruption, reduction and discontinuation recommendations in patients with relapsed or refractory AML

Criteria	Xospata dosing
Differentiation syndrome	• If differentiation syndrome is suspected, administer corticosteroids and initiate hemodynamic montoring. • Interrupt gilteritinib if severe signs and/or symptoms persist for more than 48 hours after initiation of corticosteroids. • Resume gilteritinib at the same dose when signs and symptoms improve to Grade 2[a] or lower.
Posterior reversible encephalopathy syndrome	• Discontinue gilteritinib.
QTcF interval >500 msec	• Interrupt gilteritinib. • Resume gilteritinib at a reduced dose (80 mg or 120 mg[b]) when QTcF interval returns to within 30 msec of baseline or ≤480 msec.
QTcF interval increased by >30 msec on ECG on day 8 of cycle 1	• Confirm with ECG on day 9. • If confirmed, consider dose reduction to 80 mg.
Pancreatitis	• Interrupt gilteritinib until pancreatitis is resolved. • Resume treatment with gilteritimb at a reduced dose (80 mg or 120 mg[b]).
Other Grade 3[a] or higher toxicity considered related to treatment.	• Interrupt gilteritinib until toxicity resolves or improves to Grade 1[a]. • Resume treatment with gilteritinib at a reduced dose (80 mg or 120 mg[b]).
Planned HSCT	• Interrupt treatment with gilteritinib one week prior to administration of the conditioning regimen for HSCT. • Treatment can be resumed 30 days after HSCT if engraftment was successful, the patient did not have grade ≥2 acute graft versus host disease and was in CRc[c].

a. Grade 1 is mild, Grade 2 is moderate, Grade 3 is severe, Grade 4 is life-threatening.
b. The daily dose can be reduced from 120 mg to 80 mg or from 200 mg to 120 mg.
c. 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 all criteria for CR except for incomplete haematological recovery with residual neutropenia <1 x 10^9/L with or without complete platelet recovery).

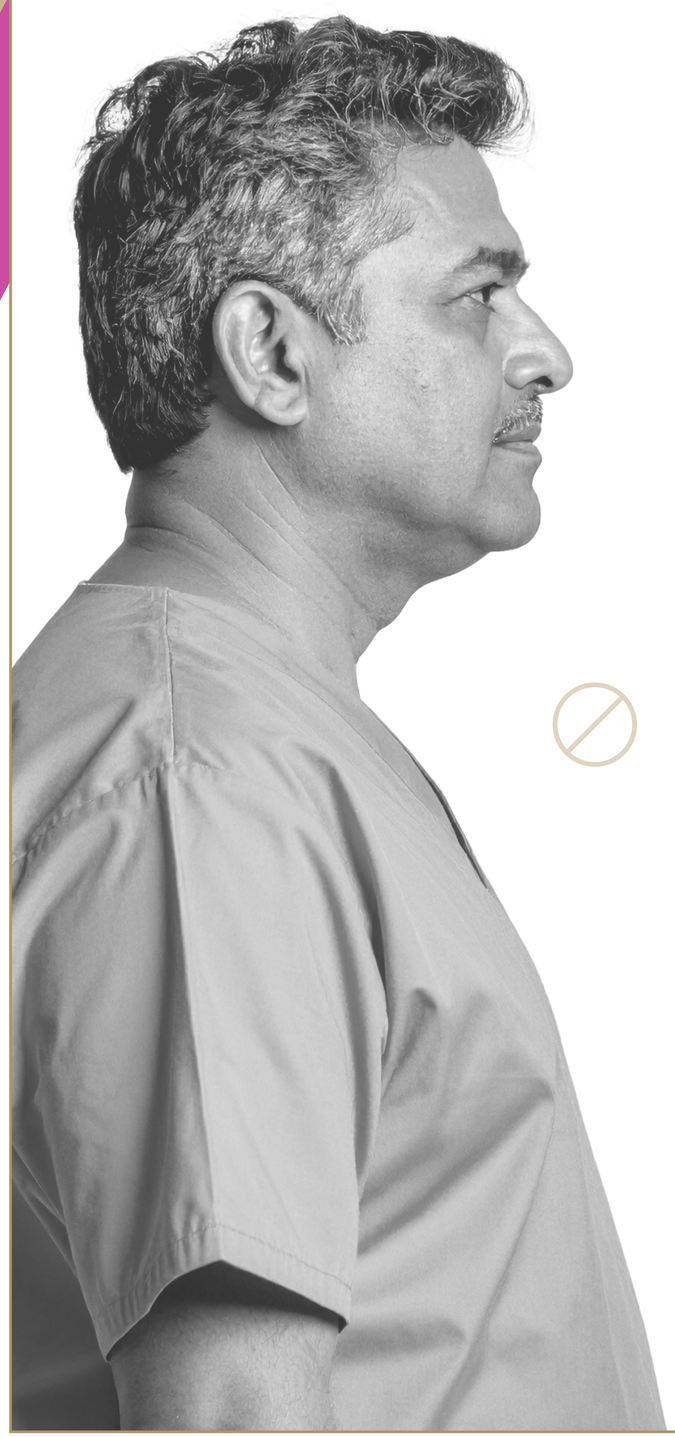
Xospata dose interruption, reduction and discontinuation recommendations in patients with relapsed or refractory AML

Should be **administered at about the same time each day.**



If a dose is missed or not taken at the usual time - Dose should be administered as soon as possible on the same day, and patients should return to the normal 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.



Elderly

- No dose adjustment required in patients ≥65 years of age.

Paediatric population

- Safety and efficacy of Xospata in children aged below 18 years – Not yet established.
- No data available. Due to in vitro binding to 5HT2B - Potential impact on cardiac development in patients less than 6 months of age.

Hepatic impairment

- No dose adjustment required for patients with mild (Child-Pugh Class A) or moderate (Child-Pugh Class B) hepatic impairment.
- Not recommended for use in patients with severe (Child-Pugh Class C) hepatic impairment - Safety and efficacy have not been evaluated in this population.

Method of administration

- **Xospata is for oral use.**
- **Tablets can be taken with or without food.**
- **Should be swallowed whole with water.**
- **Should not be broken or crushed.**

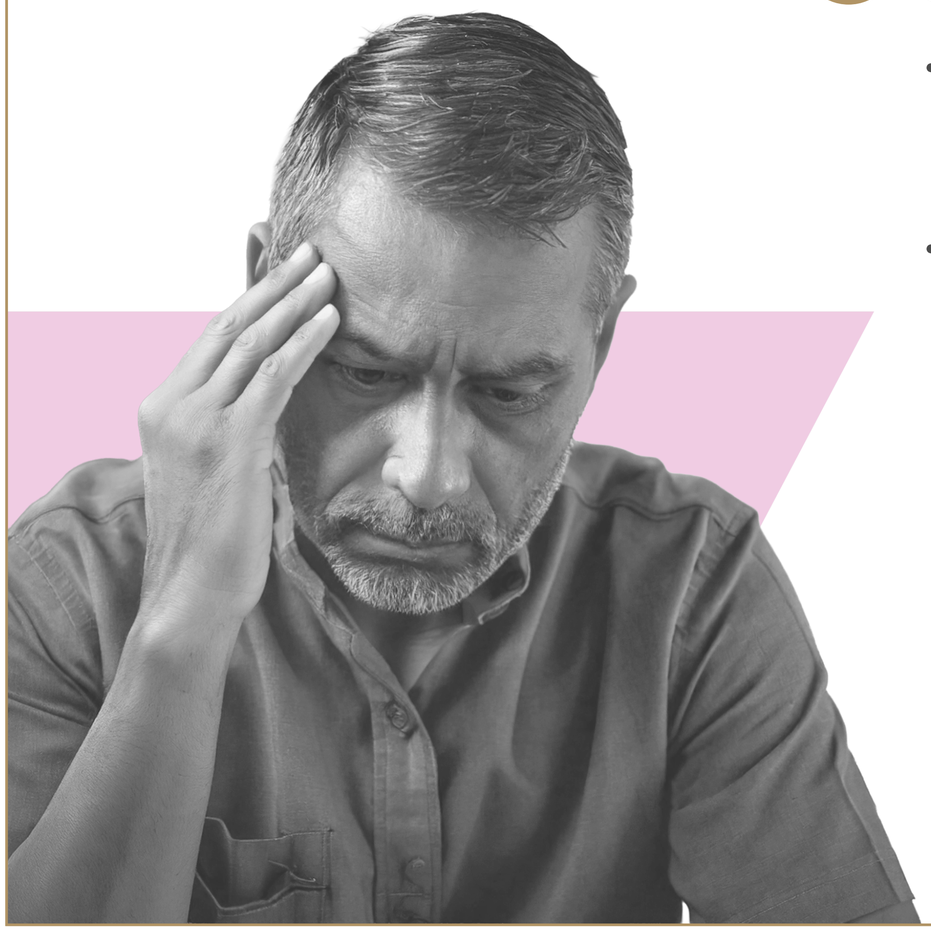
Renal impairment

- No dose adjustment necessary in patients with mild or moderate renal impairment.
- No clinical experience in patients with severe renal impairment.

Contraindications

Hypersensitivity to the active substance or to any of the excipients

Special warnings and precautions for use



Differentiation syndrome

- Gilteritinib has been associated with differentiation syndrome.
- Differentiation syndrome - Associated with rapid proliferation and differentiation of myeloid cells - May be life-threatening or fatal if not treated.

Posterior reversible encephalopathy syndrome

- There have been reports of posterior reversible encephalopathy syndrome (PRES) in patients receiving Xospata.
- PRES - Rare, reversible, neurological disorder - Can present with rapidly evolving symptoms including seizure, headache, confusion, visual and neurological disturbances, with or without associated hypertension and altered mental status.

Prolonged QT interval

- Gilteritinib has been associated with prolonged cardiac ventricular repolarisation (QT Interval). QT prolongation can be observed in the first three months of treatment.
- Caution warranted in patients with relevant cardiac history.
- Hypokalaemia or hypomagnesaemia may increase QT prolongation risk. Hypokalaemia or hypomagnesaemia should therefore be corrected prior to and during Xospata treatment.
- Decision to re-introduce gilteritinib treatment after an event of QT prolongation should be based on careful consideration of benefits and risks.
- If Xospata is re-introduced at a reduced dose, ECG should be performed after 15 days of dosing, and prior to the start of the next three subsequent months of treatment.

Pancreatitis

- There have been reports of pancreatitis.
- Patients who develop signs and symptoms suggestive of pancreatitis should be evaluated and monitored.
- Xospata should be interrupted and can be resumed at a reduced dose when the signs and symptoms of pancreatitis have resolved.

Interactions

- Co-administration of CYP3A/P-gp inducers may lead to decreased gilteritinib exposure - Consequently a risk for lack of efficacy. - Concomitant use of gilteritinib with strong CYP3A4/P-gp inducers should be avoided.
- Caution is required when concomitantly prescribing gilteritinib with strong inhibitors of CYP3A, P-gp and/or breast cancer resistant protein (BCRP) (such as, but not limited to, voriconazole, itraconazole, posaconazole and clarithromycin) - Can increase gilteritinib exposure. Alternative medicinal products that do not strongly inhibit CYP3A, P-gp and/or BCRP activity should be considered.
- Where satisfactory therapeutic alternatives do not exist - Patients should be closely monitored for toxicities during administration of Gilteritinib.
- Gilteritinib may reduce the effects of medicinal products that target 5HT2B receptor or sigma nonspecific receptors (eg. escitalopram, fluoxetine, sertraline). - Concomitant use of gilteritinib with these products should be avoided unless use is considered essential for the care of the patients.
- Gilteritinib is an inhibitor of P-gp, BCRP and OCT1 in vitro. As no clinical data is available, it cannot be excluded that gilteritinib could inhibit these transporters at a therapeutic dose. Caution is advised during co-administration of gilteritinib with substrates of P-gp (e.g., digoxin, dabigatran etexilate), BCRP (e.g., mitoxantrone, methotrexate, rosuvastatin) and OCT1 (e.g., metformin).

Embryofoetal toxicity and contraception

Fertility, pregnancy and lactation

Women of childbearing potential / Contraception in males and females

- Pregnancy testing - Recommended for females of reproductive potential seven days prior to initiating Xospata treatment.
- Women of childbearing potential - Recommended to use effective contraception (methods that result in less than 1% pregnancy rates) during and up to 6 months after treatment.
- It is unknown whether gilteritinib may reduce the effectiveness of hormonal contraceptives, therefore women using hormonal contraceptives should add a barrier method of contraception.
- Males of reproductive potential - Advised to use effective contraception during treatment and for at least 4 months after the last dose.

Pregnancy

- Gilteritinib can cause foetal harm when administered to pregnant women. There are no or limited amount of data from the use of gilteritinib in pregnant women.
- Reproductive studies in rats - gilteritinib caused suppressed foetal growth, embryo-foetal deaths and teratogenicity.
- Xospata not recommended during pregnancy and in women of childbearing potential not using effective contraception.
- Pregnant women should be informed of the potential risk to a foetus.
- Females of reproductive potential should be advised to have a pregnancy test within seven days prior to starting treatment and to use effective contraception during treatment and for at least 6 months after stopping treatment.
- Women using hormonal contraceptives - Add a barrier method of contraception.
- Males with female partners of reproductive potential - Advised to use effective contraception during treatment and for at least 4 months after the last dose.

Breast-feeding

- Unknown whether gilteritinib or its metabolites are excreted in human milk.
- Available animal data - Excretion of gilteritinib and its metabolites in the animal milk of lactating rats and distribution to the tissues in infant rats via the milk.
- Risk to breast-fed children cannot be excluded. Breast-feeding should be discontinued during treatment and for at least two months after the last dose.

Fertility

No data on the effect of gilteritinib on human fertility.

Adverse Reactions

Adverse drug reaction	All Grades %	Grades ≥ 3%	Frequency category
Immune system disorders			
Anaphylactic reaction	1.3	1.3	Common
Nervous system disorders			
Dizziness	20.4	0.3	Very common
Posterior reversible encephalopathy syndrome	0.6	0.6	Uncommon
Cardiac disorders			
Electrocardiogram QT prolonged	8.8	2.5	Common
Pericardial effusion	4.1	0.9	Common
Pericarditis	1.6	0	Common
Cardiac failure	1.3	1.3	Common
Vascular disorders			
Hypotension	17.2	7.2	Very common
Respiratory, thoracic and mediastinal disorders			
Cough	28.2	0.3	Very common
Dyspnoea	24.1	4.4	Very common
Differentiation syndrome	3.4	2.2	Common
Gastrointestinal disorders			
Diarrhoea	35.1	4.1	Very common
Nausea	29.8	1.9	Very common
Constipation	28.2	0.6	Very common

*Frequency is based on central laboratory values.

Adverse drug reaction	All Grades %	Grades ≥ 3%	Frequency category
Hepatobiliary disorders			
Alanine aminotransferase increased*	82.1	12.9	Very common
Aspartate aminotransferase increased*	80.6	10.3	Very common
Musculoskeletal and connective tissue disorders			
Blood creatine phosphokinase increased*	53.9	6.3	Very common
Blood alkaline phosphatase increased*	68.7	1.6	Very common
Pain in extremity	14.7	0.6	Very common
Arthralgia	12.5	1.3	Very common
Myalgia	12.5	0.3	Very common
Musculoskeletal pain	4.1	0.3	Common
Renal and urinary disorders			
Acute kidney injury	6.6	2.2	Common
General disorders and administration site conditions			
Fatigue	30.4	3.1	Very common
Peripheral oedema	24.1	0.3	Very common
Asthenia	13.8	2.5	Very common
Malaise	4.4	0	Common

*Frequency is based on central laboratory values.

Scan here for XOSPATA PI

For the use of registered medical practitioners only.
Additional information available on request.

Report any adverse events to Astellas Pharma India Pvt. Ltd. at **pv@in.astellas.com.**

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