XOSPATA®
gilteritinib 40mg tablets

Dosage Recommendations for Treatment With Once-Daily XOSPATA in FLT3m+ R/R AML[1]

XOSPATA is the only FDA-approved oral treatment for R/R FLT3m+ AML[1,2]

AML=acute myeloid leukemia; FDA=Food and Drug Administration; FLT3=FMS-like tyrosine kinase 3; m+=mutation-positive; R/R=relapsed or refractory.

INDICATION AND SELECT SAFETY INFORMATION

WARNING: DIFFERENTIATION SYNDROME

Patients treated with XOSPATA have experienced symptoms of differentiation syndrome, which can be fatal or life-threatening if not treated. Symptoms may include fever, dyspnea, hypoxia, pulmonary infiltrates, pleural or pericardial effusions, rapid weight gain or peripheral edema, hypotension, or renal dysfunction. If differentiation syndrome is suspected, initiate corticosteroid therapy and hemodynamic monitoring until symptom resolution.

INDICATION

XOSPATA is indicated for the treatment of adult patients who have relapsed or refractory acute myeloid leukemia (AML) with a FMS-like tyrosine kinase 3 (FLT3) mutation as detected by an FDA-approved test.

CONTRAINDICATIONS

XOSPATA is contraindicated in patients with hypersensitivity to gilteritinib or any of the excipients. Anaphylactic reactions have been observed in clinical trials.

Please see additional Important Safety Information on pages 5-6 and click here for Full Prescribing Information, including BOXED WARNING.

Offer Patients a Once-Daily Oral Therapy With XOSPATA[1]

The recommended starting dose of XOSPATA[1]:

120 mg
once daily

Three 40 mg tablets

Tablets shown are not actual size.

With or without food

- XOSPATA may be taken at home[1]
- Administer XOSPATA tablets orally at about the same time each day[1]
- Do not break, chew, or crush XOSPATA tablets. Take whole with a cup of water[1]
- If a dose of XOSPATA is missed or not taken at the usual time[1]:
  - Administer the dose as soon as possible on the same day, and at least 12 hours prior to the next scheduled dose
  - Return to the normal schedule the following day
  - Do not administer 2 doses within 12 hours

Allowing time for a clinical response

- Response may be delayed. In the absence of disease progression or unacceptable toxicity, treatment for a minimum of 6 months is recommended to allow time for a clinical response[1]

The 120-mg dose of XOSPATA was studied and demonstrated efficacy in the ADMIRAL pivotal trial[1]*

*XOSPATA was given orally at a starting dose of 120 mg daily until unacceptable toxicity or lack of clinical benefit.[1]

SELECT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

Differentiation Syndrome (See BOXED WARNING) 3% of 319 patients treated with XOSPATA in the clinical trials experienced differentiation syndrome. Differentiation syndrome is associated with rapid proliferation and differentiation of myeloid cells and may be life-threatening or fatal if not treated. Symptoms and other clinical findings of differentiation syndrome in patients treated with XOSPATA included 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. Differentiation syndrome occurred as early as 1 day and up to 82 days after XOSPATA initiation and has been observed with or without concomitant leukocytosis. If differentiation syndrome is suspected, initiate dexamethasone 10 mg IV every 12 hours (or an equivalent dose of an alternative oral or IV corticosteroid) and hemodynamic monitoring until improvement. Taper corticosteroids after resolution of symptoms and administer corticosteroids for a minimum of 3 days. Symptoms of differentiation syndrome may recur with premature discontinuation of corticosteroid treatment. If severe signs and/or symptoms persist for more than 48 hours after initiation of corticosteroids, interrupt XOSPATA until signs and symptoms are no longer severe.

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Monitoring and Dosage Modifications

Monitoring[1]

- Assess blood counts and blood chemistries, including creatine phosphokinase:
  - Prior to initiating treatment with XOSPATA
  - At least once a week for the first month
  - Once every other week for the second month
  - Once monthly for the duration of therapy
- Perform an ECG prior to initiation of treatment with XOSPATA, on Days 8 and 15 of the first cycle, and prior to the start of the next 2 subsequent cycles

Dosage modifications for XOSPATA-related toxicities[1]

- **Differentiation syndrome:** If differentiation syndrome is suspected, administer systemic corticosteroids and initiate hemodynamic monitoring until symptom resolution and for a minimum of 3 days. Interrupt XOSPATA if severe signs and/or symptoms persist for more than 48 hours after initiation of corticosteroids and resume XOSPATA when signs and symptoms improve to Grade 2 or lower†
- **Posterior reversible encephalopathy syndrome:** Discontinue XOSPATA
- **QTc interval >500 msec:** Interrupt XOSPATA and resume at 80 mg dose when QTc interval returns to within 30 msec of baseline or ≤480 msec
- **QTc interval increased by >30 msec on ECG on Day 8 of first cycle:** Confirm with ECG on Day 9 and, if confirmed, consider dose reduction to 80 mg
- **Pancreatitis:** Interrupt XOSPATA until pancreatitis is resolved and resume at 80 mg dose
- **Other Grade ≥3 toxicity considered related to treatment:** Interrupt XOSPATA until toxicity resolves or improves to Grade 1† and resume at 80 mg dose

Patients in the XOSPATA arm were randomized to receive the approved and recommended starting dose of 120 mg once daily[1]

†Grade 1 is mild, Grade 2 is moderate, Grade 3 is serious, Grade 4 is life-threatening.[1]

ECG=electrocardiogram; QT=cardiac ventricular repolarization; QTc=corrected QT.

SELECT SAFETY INFORMATION

Posterior Reversible Encephalopathy Syndrome (PRES) 1% of 319 patients treated with XOSPATA in the clinical trials experienced posterior reversible encephalopathy syndrome (PRES) with symptoms including seizure and altered mental status. Symptoms have resolved after discontinuation of XOSPATA. A diagnosis of PRES requires confirmation by brain imaging, preferably magnetic resonance imaging (MRI). Discontinue XOSPATA in patients who develop PRES.

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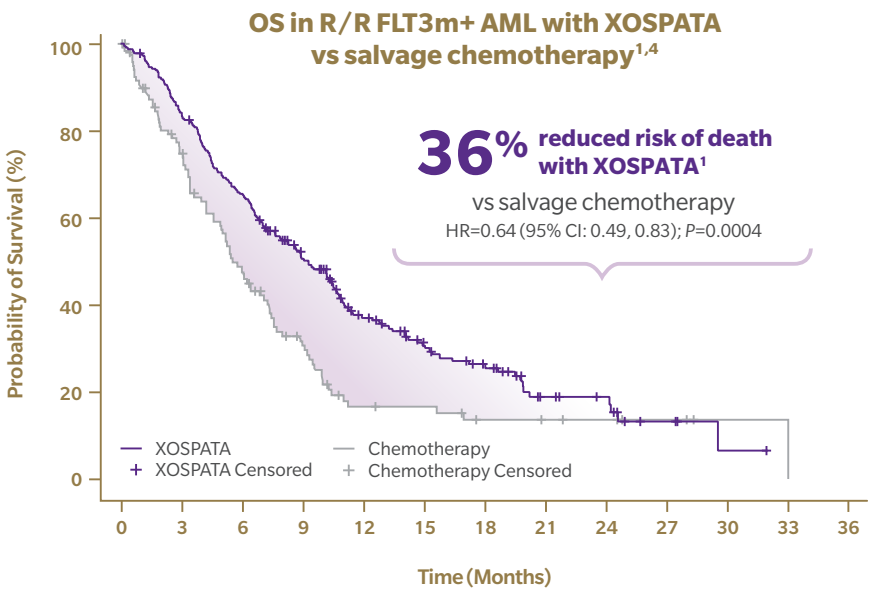
Superior OS Observed in R/R FLT3m+ AML With XOSPATA vs Salvage Chemotherapy[1]*

- XOSPATA was evaluated in a Phase 3, open-label, multicenter, randomized clinical trial compared with a prespecified salvage chemotherapy in adult patients with R/R FLT3m+ AML.[1,3] Prespecified chemotherapy regimens included high-intensity combinations MEC† and FLAG-IDA‡ and low-intensity regimens LDAC§ and AZA‖[1]

Primary endpoint: OS (intention-to-treat population)[1,4]



Number of Patients at Risk

XOSPATA	247	206	157	106	64	44	31	14	11	4	1	0	0
Chemotherapy	124	84	52	29	13	12	8	7	5	3	1	0	0

The Kaplan-Meier method, in combination with the Greenwood formula, was used to determine OS and corresponding 95% CIs.[4]

9.3 MONTHS

median OS with XOSPATA**
(95% CI: 7.7, 10.7)[1]

vs 5.6 months median OS with salvage chemotherapy**
(95% CI: 4.7, 7.3)[1]

90% of all patients in the ADMIRAL trial had *FLT3-ITD*-mutated R/R AML (n=335/371)[1¶#]

- 31 out of 371 patients had a *FLT3-TKD* mutation alone (n=31/371)

*FLT3 mutation status: *FLT3-ITD*, *FLT3-TKD*, and *FLT3-ITD-TKD*.[1]

†MEC: Mitoxantrone 8 mg/m^2, etoposide 100 mg/m^2, and cytarabine 1000 mg/m^2 once daily by IV infusion Days 1-5.[1]

‡FLAG-IDA: Granulocyte colony-stimulating factor 300 mcg/m^2 once daily by SC injection Days 1-5, fludarabine 30 mg/m^2 once daily by IV infusion Days 2-6, cytarabine 2000 mg/m^2 once daily by IV infusion Days 2-6, idarubicin 10 mg/m^2 once daily by IV infusion Days 2-4.[1]

§LDAC: Cytarabine 20 mg twice daily by SC injection or IV infusion for 10 days.[1]

‖AZA: Azacitidine 75 mg/m^2 once daily by SC injection or IV infusion for 7 days.[1]

**Median OS was based on Kaplan-Meier estimates.[5]

¶The remaining 5 patients were negative by the diagnostic test.[5]

#This includes 7 patients with both ITD and TKD mutations.[1]

AML=acute myeloid leukemia; FLT3=FMS-like tyrosine kinase 3; HR=hazard ratio; ITD=internal tandem duplication; IV=intravenous; m+=mutation-positive; OS=overall survival; R/R=relapsed or refractory; SC=subcutaneous; TKD=tyrosine kinase domain.

The recommended starting dose of XOSPATA is 120 mg once daily. If XOSPATA-related toxicities occur after initiating treatment, refer to dosage modifications above[1]

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Indication and Important Safety Information

INDICATION

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IMPORTANT SAFETY INFORMATION

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Prolonged QT Interval XOSPATA has been associated with prolonged cardiac ventricular repolarization (QT interval). 1% of the 317 patients with a post-baseline QTc measurement on treatment with XOSPATA in the clinical trial were found to have a QTc interval greater than 500 msec and 7% of patients had an increase from baseline QTc greater than 60 msec. Perform electrocardiogram (ECG) prior to initiation of treatment with XOSPATA, on days 8 and 15 of cycle 1, and prior to the start of the next two subsequent cycles. Interrupt and reduce XOSPATA dosage in patients who have a QTcF >500 msec. Hypokalemia or hypomagnesemia may increase the QT prolongation risk. Correct hypokalemia or hypomagnesemia prior to and during XOSPATA administration.

Pancreatitis 4% of 319 patients treated with XOSPATA in the clinical trials experienced pancreatitis. Evaluate patients who develop signs and symptoms of pancreatitis. Interrupt and reduce the dose of XOSPATA in patients who develop pancreatitis.

Embryo-Fetal Toxicity XOSPATA can cause embryo-fetal harm when administered to a pregnant woman. Advise females of reproductive potential to use effective contraception during treatment with XOSPATA and for 6 months after the last dose of XOSPATA. Advise males with female partners of reproductive potential to use effective contraception during treatment with XOSPATA and for 4 months after the last dose of XOSPATA. Pregnant women, patients becoming pregnant while receiving XOSPATA or male patients with pregnant female partners should be apprised of the potential risk to the fetus.

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Indication and Important Safety Information (cont'd.)

ADVERSE REACTIONS

Fatal adverse reactions occurred in 2% of patients receiving XOSPATA. These were cardiac arrest (1%) and one case each of differentiation syndrome and pancreatitis. The most frequent (≥5%) nonhematological serious adverse reactions reported in patients were fever (13%), dyspnea (9%), renal impairment (8%), transaminase increased (6%) and noninfectious diarrhea (5%).

7% discontinued XOSPATA treatment permanently due to an adverse reaction. The most common (>1%) adverse reactions leading to discontinuation were aspartate aminotransferase increased (2%) and alanine aminotransferase increased (2%).

The most frequent (≥5%) grade ≥3 nonhematological adverse reactions reported in patients were transaminase increased (21%), dyspnea (12%), hypotension (7%), mucositis (7%), myalgia/arthralgia (7%), and fatigue/malaise (6%).

Other clinically significant adverse reactions occurring in ≤10% of patients included: electrocardiogram QT prolonged (9%), hypersensitivity (8%), pancreatitis (5%), cardiac failure (4%), pericardial effusion (4%), acute febrile neutrophilic dermatosis (3%), differentiation syndrome (3%), pericarditis/myocarditis (2%), large intestine perforation (1%), and posterior reversible encephalopathy syndrome (1%).

Lab Abnormalities Shifts to grades 3-4 nonhematologic laboratory abnormalities in XOSPATA treated patients included phosphate decreased (14%), alanine aminotransferase increased (13%), sodium decreased (12%), aspartate aminotransferase increased (10%), calcium decreased (6%), creatine kinase increased (6%), triglycerides increased (6%), creatinine increased (3%), and alkaline phosphatase increased (2%).

DRUG INTERACTIONS

Combined P-gp and Strong CYP3A Inducers Concomitant use of XOSPATA with a combined P-gp and strong CYP3A inducer decreases XOSPATA exposure which may decrease XOSPATA efficacy. Avoid concomitant use of XOSPATA with combined P-gp and strong CYP3A inducers.

Strong CYP3A inhibitors Concomitant use of XOSPATA with a strong CYP3A inhibitor increases XOSPATA exposure. Consider alternative therapies that are not strong CYP3A inhibitors. If the concomitant use of these inhibitors is considered essential for the care of the patient, monitor patient more frequently for XOSPATA adverse reactions. Interrupt and reduce XOSPATA dosage in patients with serious or life-threatening toxicity.

Drugs that Target 5HT2B Receptor or Sigma Nonspecific Receptor Concomitant use of XOSPATA may reduce the effects of drugs that target the 5HT2B receptor or the sigma nonspecific receptor (e.g., escitalopram, fluoxetine, sertraline). Avoid concomitant use of these drugs with XOSPATA unless their use is considered essential for the care of the patient.

P-gp, BCRP, and OCT1 Substrates Based on *in vitro* data, gilteritinib is a P-gp, breast cancer resistant protein (BCRP), and organic cation transporter 1 (OCT1) inhibitor. Coadministration of gilteritinib may increase the exposure of P-gp, BCRP, and OCT1 substrates, which may increase the incidence and severity of adverse reactions of these substrates. For P-gp, BCRP, or OCT1 substrates where small concentration changes may lead to serious adverse reactions, decrease the dose or modify the dosing frequency of such substrate and monitor for adverse reactions as recommended in the respective prescribing information.

SPECIFIC POPULATIONS

Lactation Advise women not to breastfeed during treatment with XOSPATA and for 2 months after the last dose.

Please see Full Prescribing Information including BOXED WARNING for additional safety information.

For important state pricing disclosure information, click **here**.

References: 1. XOSPATA [package insert]. Northbrook, IL: Astellas Pharma US, Inc. **2.** Ballesta-López O, Solana-Altabella A, Megías-Vericat JE, Martínez-Cuadrón D, Montesinos P. Gilteritinib use in the treatment of relapsed or refractory acute myeloid leukemia with a FLT3 mutation. Future Oncol 2021;17(2):215-227. **3.** ClinicalTrials.gov. A study of ASP2215 versus salvage chemotherapy in patients with relapsed or refractory acute myeloid leukemia (AML) with FMS-like tyrosine kinase (FLT3) mutation. Updated April 25, 2024. Accessed May 15, 2024. https://www.clinicaltrials.gov/study/NCT02421939. **4.** 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. Erratum in: N Engl J Med 2022;386(19):1868. **5.** Astellas. XOSPATA. Data on File.

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To find out how Astellas is changing the course of cancer treatment, please visit **astellasoncology.com**

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