XOSPATA Is the First FDA-Approved FLT3 Inhibitor Indicated for Patients with Relapsed or Refractory FLT3m+ Acute Myeloid Leukemia (AML)[1]

XOSPATA® gilteritinib 40mg tablets

Dear Customer,

Astellas Pharma US, Inc. is pleased to announce that the FDA has approved XOSPATA. 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.[1] An estimated 37% of AML patients have a FLT3 mutation and are considered at higher risk for relapsed or refractory disease.[2-4] Patients with relapsed or refractory FLT3m+ AML have limited therapeutic options and are challenging to treat.[3,5]

XOSPATA was evaluated in a pre-planned interim analysis that included 138 patients randomized to the XOSPATA arm.[1,6] Efficacy was established on the basis of complete remission (CR)/complete remission with partial hematologic recovery (CRh) rate, DOR and rate of conversion from transfusion dependence to transfusion independence.[1] OS data were not mature at the time of the pre-planned interim analysis.[7]

XOSPATA demonstrated the ability to inhibit FLT3 receptor signaling and proliferation in cells exogenously expressing FLT3 mutations, including[1]*:

FLT3-ITD	*FLT3-TKD* (FLT3-D835Y)	*FLT3-ITD* and *FLT3-TKD* (FLT3-ITD-D835Y)

XOSPATA is an oral monotherapy[1]

*The clinical significance of the preclinical studies is unknown.

In the ADMIRAL trial

21.0% **of patients** treated with XOSPATA **achieved CR†/CRh‡** (95% CI, 14.5-28.8; n=29/138)[1]

- Median DOR§ was 4.6 months (range: 0.1 to 15.8 months‖)[1]

31.1% **of patients converted to transfusion independence** during any 56-day post-baseline period among patients who were transfusion dependent at baseline (n=33/106)[1¶]

8% **of patients** treated with XOSPATA **permanently discontinued treatment** due to an adverse reaction (N=22/292)[1]

†**CR was defined as normal marrow differential with <5% blasts, ANC ≥1.0 × 10^9/L and platelets ≥100 × 10^9/L, no evidence of extramedullary leukemia and must have been RBC and platelet transfusion independent.**

‡**CRh was defined as marrow blasts <5%, partial hematologic recovery, ANC ≥0.5 × 10^9/L and platelets ≥50 × 10^9/L, no evidence of extramedullary leukemia and could not have been classified as CR.**[1]

§DOR was defined as the time from the date of either first CR or CRh until the date of a documented relapse of any type, with deaths counted as events.[1]

‖Response was ongoing.[1]

¶Among patients who were transfusion dependent on RBC and/or platelets at baseline. Transfusion independence is defined as patients who were dependent on RBC and/or platelet transfusions at baseline and became independent of RBC and platelet transfusions during any 56-day post-baseline period.[1]

ANC, absolute neutrophil count; DOR, duration of CR/CRh; FDA, Food and Drug Administration; FLT3, FMS-like tyrosine kinase 3; FLT3m+, FLT3 mutation-positive; ITD, internal tandem duplication; OS, overall survival; RBC, red blood cell; TKD, tyrosine kinase domain

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.

For additional details regarding XOSPATA, please contact your XOSPATA Account Manager.

Select Safety Information

Contraindications

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

Warnings and Precautions

Posterior Reversible Encephalopathy Syndrome (PRES) There have been rare reports of PRES with symptoms including seizure and altered mental status with XOSPATA. Symptoms have resolved after discontinuation of XOSPATA. A diagnosis of PRES requires confirmation by brain imaging, preferably MRI. Discontinue XOSPATA in patients who develop PRES.

Prolonged QT Interval XOSPATA has been associated with prolonged cardiac ventricular repolarization (QT interval). Of the 292 patients treated with XOSPATA in the clinical trial, 1.4% 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.

Please see continuing Important Safety Information on the next page. Click here for full Prescribing Information.

Important Safety Information (cont'd)

Warnings and Precautions (cont'd)

Pancreatitis There have been rare reports of pancreatitis in patients receiving XOSPATA in clinical studies. Evaluate patients who develop signs and symptoms of pancreatitis. Interrupt and reduce the dose of XOSPATA in patients who develop pancreatitis.

Embryo-Fetal Toxicity Based on findings in animals and its mechanism of action, 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 at least 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 at least 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.

Adverse Reactions

The most frequent non-hematological serious adverse reactions (≥5%) reported in patients were pneumonia (19%), sepsis (13%), fever (13%), dyspnea (7%) and renal impairment (5%).

Overall, 22 of 292 patients (8%) discontinued XOSPATA treatment permanently due to an adverse reaction. The most common adverse reactions (>1%) leading to discontinuation were pneumonia (2%), sepsis (2%) and dyspnea (1%). The most common adverse reactions (≥20%) were myalgia/arthralgia (42%), transaminase increased (41%), fatigue/malaise (40%), fever (35%), non-infectious diarrhea (34%), dyspnea (34%), edema (34%), rash (30%), pneumonia (30%), nausea (27%), stomatitis (26%), cough (25%), headache (21%), hypotension (21%), dizziness (20%) and vomiting (20%).

Other clinically significant adverse reactions occurring in ≤10% of patients included: electrocardiogram QT prolonged (7%), cardiac failure (grouped terms) (4%), pericardial effusion (3%), pericarditis (2%), differentiation syndrome (1%), anaphylactic reaction (1%) and posterior reversible encephalopathy syndrome (1%).

Lab Abnormalities: The most common lab abnormalities (>20%) that were Grade ≥3 that occurred ≥10% were: hypophosphatemia (12%), alanine aminotransferase increased (12%), hyponatremia (12%), aspartate aminotransferase increased (10%).

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.

Specific Populations

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

Click here for full Prescribing Information.

Kind regards,

Astellas Health Systems

References: 1. XOSPATA [package insert]. Northbrook, IL: Astellas Pharma US, Inc. **2.** Patel JP, Gönen M, Figueroa ME, et al. Prognostic relevance of integrated genetic profiling in acute myeloid leukemia. N Engl J Med 2012;366(12):1079-89. **3.** Wagner K, Damm F, Thol F, et al. FLT3-internal tandem duplication and age are the major prognostic factors in patients with relapsed acute myeloid leukemia with normal karyotype. Haematologica 2011;96(5):681-6. **4.** Brunet S, Labopin M, Esteve J, et al. Impact of FLT3 internal tandem duplication on the outcome of related and unrelated hematopoietic transplantation for adult acute myeloid leukemia in first remission: a retrospective analysis. J Clin Oncol 2012;30(7):735-41. **5.** Chevallier P, Labopin M, Turlure P, et al. A new leukemia prognostic scoring system for refractory/relapsed adult acute myelogeneous leukaemia patients: a GOELAMS study. Leukemia 2011;25(6):939-44. **6.** Astellas. XOSPATA. Data on File. **7.** 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 (04-25-2018). https://clinicaltrials.gov/ct2/show/NCT02421939. Accessed 04-26-2018.

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