

XOSPATA- gilteritinib tablet
Astellas Pharma US, Inc.

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use XOSPATA safely and effectively. See full prescribing information for XOSPATA.

XOSPATA® (gilteritinib) tablets, for oral use
Initial U.S. Approval: 2018

WARNING: DIFFERENTIATION SYNDROME

See full prescribing information for complete boxed warning.

Patients treated with XOSPATA have experienced symptoms of differentiation syndrome, which can be fatal if not treated. If differentiation syndrome is suspected, initiate corticosteroid therapy and hemodynamic monitoring until symptom resolution. (5.1, 6.1)

INDICATIONS AND USAGE

XOSPATA is a kinase inhibitor indicated for the treatment of adult patients who have relapsed or refractory acute myeloid leukemia (AML) with a FLT3 mutation as detected by an FDA-approved test. (1.1)

DOSAGE AND ADMINISTRATION

120 mg orally once daily. (2.2)

DOSAGE FORMS AND STRENGTHS

Tablets: 40 mg. (3)

CONTRAINDICATIONS

Hypersensitivity to gilteritinib or any of the excipients. Anaphylactic reactions have been observed in clinical trials. (4, 6.1)

WARNINGS AND PRECAUTIONS

- Posterior reversible encephalopathy syndrome (PRES): Discontinue XOSPATA in patients who develop PRES. (2.3, 5.2, 6.1)
- Prolonged QT Interval: Interrupt and reduce XOSPATA dosage in patients who have a QTcF >500 msec. Correct hypokalemia or hypomagnesemia prior to and during XOSPATA administration. (2.3, 5.3, 12.2, 6.1)
- Pancreatitis: Interrupt and reduce the dose in patients who develop pancreatitis. (2.3, 5.4)
- Embryo-Fetal Toxicity: XOSPATA can cause fetal harm when administered to a pregnant woman. Advise of the potential risk to a fetus and to use effective contraception. (5.5, 8.1, 8.3)

ADVERSE REACTIONS

The most common adverse reactions ($\geq 20\%$) are transaminase increased, myalgia/arthralgia, fatigue/malaise, fever, mucositis, edema, rash, noninfectious diarrhea, dyspnea, nausea, cough, constipation, eye disorders, headache, dizziness, hypotension, vomiting, and renal impairment. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Astellas Pharma US, Inc. at 1-800-727-7003 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- Combined P-gp and Strong CYP3A Inducers: Avoid concomitant use. (7.1)
- Strong CYP3A Inhibitors: Consider alternative therapies. If the concomitant use of strong CYP3A inhibitors cannot be avoided, monitor patients more frequently for XOSPATA adverse reactions. (2.3, 7.1)
- P-gp, BCRP, OCT1 Substrates: Decrease the dose of the substrates when coadministered with gilteritinib and as clinically indicated. (7.2)

USE IN SPECIFIC POPULATIONS

Lactation: Advise women not to breastfeed. (8.2)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

FULL PRESCRIBING INFORMATION: CONTENTS*

WARNING: DIFFERENTIATION SYNDROME

1 INDICATIONS AND USAGE

- 1.1 Relapsed or Refractory Acute Myeloid Leukemia

2 DOSAGE AND ADMINISTRATION

- 2.1 Patient Selection
- 2.2 Recommended Dosage
- 2.3 Dosage Modifications

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

5 WARNINGS AND PRECAUTIONS

- 5.1 Differentiation Syndrome
- 5.2 Posterior Reversible Encephalopathy Syndrome
- 5.3 Prolonged QT Interval
- 5.4 Pancreatitis
- 5.5 Embryo-Fetal Toxicity

6 ADVERSE REACTIONS

- 6.1 Clinical Trials Experience

7 DRUG INTERACTIONS

- 7.1 Effect of Other Drugs on XOSPATA
- 7.2 Effect of XOSPATA on Other Drugs

8 USE IN SPECIFIC POPULATIONS

- 8.1 Pregnancy
- 8.2 Lactation
- 8.3 Females and Males of Reproductive Potential
- 8.4 Pediatric Use
- 8.5 Geriatric Use

11 DESCRIPTION

12 CLINICAL PHARMACOLOGY

- 12.1 Mechanism of Action
- 12.2 Pharmacodynamics
- 12.3 Pharmacokinetics

13 NONCLINICAL TOXICOLOGY

- 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
- 13.2 Animal Toxicology and/or Pharmacology

14 CLINICAL STUDIES

- 14.1 Relapsed or Refractory Acute Myeloid Leukemia

16 HOW SUPPLIED/STORAGE AND HANDLING

17 PATIENT COUNSELING INFORMATION

* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING 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 [see Warnings and Precautions (5.1) and Adverse Reactions (6.1)].

1 INDICATIONS AND USAGE

1.1 Relapsed or Refractory Acute Myeloid Leukemia

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.

2 DOSAGE AND ADMINISTRATION

2.1 Patient Selection

Select patients for the treatment of AML with XOSPATA based on the presence of FLT3 mutations in the blood or bone marrow [see *Clinical Studies (14)*]. Information on FDA-approved tests for the detection of a FLT3 mutation in AML is available at <http://www.fda.gov/CompanionDiagnostics>.

2.2 Recommended Dosage

The recommended starting dose of XOSPATA is 120 mg orally once daily with or without food. 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.

Do not break or crush XOSPATA tablets. Administer XOSPATA tablets orally about the same time each day. If a dose of XOSPATA is missed or not taken at the usual time, 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.

2.3 Dosage Modifications

Assess blood counts and blood chemistries, including creatine phosphokinase, prior to the initiation of XOSPATA, at least once weekly for the first month, once every other week for the second month, and once monthly for the duration of therapy. Perform electrocardiogram (ECG) prior to initiation of treatment with gilteritinib, on days 8 and 15 of cycle 1, and prior to the start of the next two subsequent cycles.

Interrupt dosing or reduce dose for toxicities as per Table 1.

Table 1: Dosage Modifications for XOSPATA-Related Toxicities*

Adverse Reaction	Recommended Action
Differentiation Syndrome	<ul style="list-style-type: none"> • If differentiation syndrome is suspected, administer systemic corticosteroids and initiate hemodynamic monitoring until symptom resolution and for a minimum of 3 days [see Warnings and Precautions (5.1)]. • Interrupt XOSPATA if severe signs and/or symptoms persist for more than 48 hours after initiation of corticosteroids [see Warnings and Precautions (5.1)]. • Resume XOSPATA when signs and symptoms improve to Grade 2* or lower.
Posterior Reversible Encephalopathy Syndrome	<ul style="list-style-type: none"> • Discontinue XOSPATA.
QTc interval greater than 500 msec	<ul style="list-style-type: none"> • Interrupt XOSPATA. • Resume XOSPATA at 80 mg when QTc interval returns to within 30 msec of baseline or less than or equal to 480 msec.
QTc interval increased by >30 msec on ECG on day 8 of cycle 1	<ul style="list-style-type: none"> • Confirm with ECG on day 9. • If confirmed, consider dose reduction to 80 mg.
Pancreatitis	<ul style="list-style-type: none"> • Interrupt XOSPATA until pancreatitis is resolved. • Resume XOSPATA at 80 mg.
Other Grade 3* or higher toxicity considered related to treatment.	<ul style="list-style-type: none"> • Interrupt XOSPATA until toxicity resolves or improves to Grade 1*. • Resume XOSPATA at 80 mg.

* Grade 1 is mild, Grade 2 is moderate, Grade 3 is serious, Grade 4 is life-threatening.

3 DOSAGE FORMS AND STRENGTHS

Tablets: 40 mg as light yellow, round-shaped, film-coated tablets debossed with the

Astellas logo and '235' on the same side.

4 CONTRAINDICATIONS

XOSPATA is contraindicated in patients with hypersensitivity to gilteritinib or any of the excipients. Anaphylactic reactions have been observed in clinical trials [see *Adverse Reactions (6) and Description (11)*].

5 WARNINGS AND PRECAUTIONS

5.1 Differentiation Syndrome

Of 319 patients treated with XOSPATA in the clinical trials, 3% 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. Of the 11 patients who experienced differentiation syndrome, 9 (82%) recovered after treatment or after dose interruption of XOSPATA.

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 [see *Dosage and Administration (2.3)*].

5.2 Posterior Reversible Encephalopathy Syndrome

Of 319 patients treated with XOSPATA in the clinical trials, 1% 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 [see *Dosage and Administration (2.3) and Adverse Reactions (6.1)*].

5.3 Prolonged QT Interval

XOSPATA has been associated with prolonged cardiac ventricular repolarization (QT interval). Of the 317 patients with a post-baseline QTc measurement on treatment with XOSPATA in the clinical trial, 1% 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 gilteritinib, 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 [see *Dosage and*

Administration (2.3), Adverse Reactions (6.1) and Clinical Pharmacology (12.2)].

Hypokalemia or hypomagnesemia may increase the QT prolongation risk. Correct hypokalemia or hypomagnesemia prior to and during XOSPATA administration.

5.4 Pancreatitis

Of 319 patients treated with XOSPATA in the clinical trials, 4% experienced pancreatitis. Evaluate patients who develop signs and symptoms of pancreatitis. Interrupt and reduce the dose of XOSPATA in patients who develop pancreatitis [*see Dosage and Administration (2.3)*].

5.5 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. In animal reproduction studies, administration of gilteritinib to pregnant rats during organogenesis caused embryo-fetal lethality, suppressed fetal growth and teratogenicity at maternal exposures (AUC_{24}) approximately 0.4 times the AUC_{24} in patients receiving the recommended dose. 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 [*see Use in Specific Populations (8.1, 8.3) and Clinical Pharmacology (12.1)*].

6 ADVERSE REACTIONS

The following clinically significant adverse reactions are described elsewhere in the labeling:

- Differentiation syndrome [*see Boxed Warning and Warnings and Precautions (5.1)*]
- Posterior reversible encephalopathy syndrome [*see Warnings and Precautions (5.2)*]
- Prolonged QT interval [*see Warnings and Precautions (5.3)*]
- Pancreatitis [*see Warnings and Precautions (5.4)*]

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The safety profile of XOSPATA is based on 319 patients with relapsed or refractory AML treated with gilteritinib 120 mg daily in three clinical trials. The median duration of exposure to XOSPATA was 3.6 months (range 0.1 to 43.4 months).

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

Of the 319 patients, 91 (29%) required a dose interruption due to an adverse reaction; the most common adverse reactions leading to dose interruption were aspartate aminotransferase increased (6%), alanine aminotransferase increased (6%) and fever (4%). Twenty patients (6%) required a dose reduction due to an adverse reaction. Twenty-two (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%).

Overall, for the 319 patients, the most frequent ($\geq 10\%$) all-grade nonhematological adverse reactions reported in patients were transaminase increased (51%), myalgia/arthralgia (50%), fatigue/malaise (44%), fever (41%), mucositis (41%), edema (40%), rash (36%), noninfectious diarrhea (35%), dyspnea (35%), nausea (30%), cough (28%), constipation (28%), eye disorders (25%), headache (24%), dizziness (22%), hypotension (22%), vomiting (21%), renal impairment (21%), abdominal pain (18%), neuropathy (18%), insomnia (15%) and dysgeusia (11%). The most frequent ($\geq 5\%$) 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%). Shifts to grades 3-4 nonhematologic laboratory abnormalities included phosphate decreased 42/309 (14%), alanine aminotransferase increased 41/317 (13%), sodium decreased 37/314 (12%), aspartate aminotransferase increased 33/317 (10%), calcium decreased 19/312 (6%), creatine kinase increased 20/317 (6%), triglycerides increased 18/310 (6%), creatinine increased 10/316 (3%), and alkaline phosphatase increased 5/317 (2%).

Adverse reactions reported in the first 30 days of therapy on the ADMIRAL Study [see *Clinical Studies (14)*] are shown in Tables 2 and 3, according to whether patients were preselected for high intensity or low intensity chemotherapy.

Table 2: Adverse Reactions Reported in $\geq 10\%$ (Any Grade) or $\geq 5\%$ (Grade 3-5)* of Patients with Relapsed or Refractory AML in the Pre-selected High Intensity Chemotherapy Subgroup in the First 30 Days of the ADMIRAL Trial

Adverse Reaction	Any Grade n (%)		Grade ≥ 3 n (%)	
	XOSPATA (120 mg daily) n=149	Chemotherapy n=68	XOSPATA (120 mg daily) n=149	Chemotherapy n=68
Musculoskeletal and connective tissue disorders				
Myalgia/arthralgia [†]	56 (38)	20 (29)	1 (1)	3 (4)
Investigations				
Transaminase increased [‡]	46 (31)	11 (16)	15 (10)	5 (7)
General disorders and administration site conditions				
Fatigue/malaise [§]	36 (24)	9 (13)	1 (1)	2 (3)
Fever	25 (17)	21 (31)	2 (1)	4 (6)
Edema [¶]	20 (13)	13 (19)	0	0
Gastrointestinal disorders				
Constipation	29 (20)	10 (15)	0	0

Mucositis [#]	18 (12)	30 (44)	0	5 (7)
Nausea	23 (15)	26 (38)	0	0
Abdominal pain ^p	16 (11)	16 (24)	0	0
Blood and lymphatic system disorder				
Febrile neutropenia	26 (17)	30 (44)	26 (17)	30 (44)
Skin and subcutaneous tissue disorders				
Rash ^β	23 (15)	21 (31)	1 (1)	2 (3)
Respiratory, thoracic and mediastinal disorders				
Dyspnea ^à	20 (13)	9 (13)	1 (1)	6 (9)
Cough	18 (12)	5 (7)	1 (1)	0
Nervous system disorders				
Neuropathy ^è	19 (13)	0	0	0
Dizziness ^ð	17 (11)	2 (3)	0	0
Headache	17 (11)	12 (18)	0	0

* Grade 3-5 includes serious, life-threatening and fatal adverse reactions

† Grouped terms: arthralgia, back pain, bone pain, flank pain, limb discomfort, medial tibial stress syndrome, myalgia, muscle twitching, musculoskeletal discomfort, musculoskeletal pain, muscle spasms, neck pain, non-cardiac chest pain, pain and pain in extremity

‡ Grouped terms: aspartate aminotransferase increased, alanine aminotransferase increased, blood alkaline phosphatase increased, gamma-glutamyltransferase increased, hepatic enzyme increased, hepatic function abnormal, hepatotoxicity, liver function test increased and transaminases increased

§ Grouped terms: asthenia, fatigue, lethargy and malaise

¶ Grouped terms: edema, edema peripheral, face edema, fluid overload, generalized edema, hypervolemia, localized edema, periorbital edema and swelling face

Grouped terms: aphthous ulcer, colitis, enteritis, esophageal pain, gingival pain, large intestinal ulcer, laryngeal inflammation, lip blister, lip ulceration, mouth hemorrhage, mouth ulceration, mucosal inflammation, oral discomfort, oral pain, oropharyngeal pain, proctalgia, stomatitis, swollen tongue, tongue discomfort and tongue ulceration

p Grouped terms: abdominal discomfort, abdominal pain, abdominal pain lower, abdominal pain upper and gastrointestinal pain

β Grouped terms: acne, dermatitis bullous, dermatitis contact, drug eruption, eczema asteatotic, erythema, hyperkeratosis, lichenoid keratosis, palmar-plantar erythrodysesthesia syndrome, rash, rash maculo-papular, rash papular, skin exfoliation, skin lesion and skin hyperpigmentation

à Grouped terms: acute respiratory distress syndrome, dyspnea, dyspnea exertional, hypoxia, pulmonary edema, respiratory failure, tachypnea and wheezing

è Grouped terms: hyperesthesia, hypoesthesia, neuralgia, neuropathy peripheral, peripheral sensory neuropathy and paresthesia

ð Grouped terms: coordination abnormal and dizziness

Table 3: Adverse Reactions Reported in ≥10% (Any Grade) or ≥5% (Grade 3-5)* of Patients with Relapsed or Refractory AML in the Pre-selected Low Intensity Chemotherapy Subgroup in the First 30 Days of the ADMIRAL Trial

Adverse Reaction	Any Grade n (%)		Grade ≥3 n (%)	
	XOSPATA (120 mg daily) n=97	Chemotherapy n=41	XOSPATA (120 mg daily) n=97	Chemotherapy n=41
Investigations				
Transaminase increased [†]	35 (36)	6 (15)	9 (9)	1 (2)

Blood and lymphatic system disorder				
Febrile neutropenia	26 (27)	5 (12)	25 (26)	5 (12)
Musculoskeletal and connective tissue disorders				
Myalgia/arthralgia [‡]	21 (22)	7 (17)	2 (2)	0
General disorders and administration site conditions				
Fatigue/malaise [§]	20 (21)	9 (22)	4 (4)	1 (2)
Edema [¶]	19 (20)	5 (12)	1 (1)	0
Fever	11 (11)	7 (17)	0	0
Gastrointestinal disorders				
Mucositis [#]	19 (20)	7 (17)	1 (1)	1 (2)
Constipation	13 (13)	5 (12)	1 (1)	0
Diarrhea	12 (12)	2 (5)	0	0
Nausea	10 (10)	7 (17)	0	0
Respiratory, thoracic and mediastinal disorders				
Dyspnea [Ⓟ]	11 (11)	2 (5)	3 (3)	2 (5)
Skin and subcutaneous tissue disorders				
Rash ^β	10 (10)	2 (5)	2 (2)	0

* Grade 3-5 includes serious, life-threatening and fatal adverse reactions

† Grouped terms: aspartate aminotransferase increased, alanine aminotransferase increased, blood alkaline phosphatase increased and transaminases increased

‡ Grouped terms: arthralgia, arthritis, back pain, limb discomfort, myalgia, muscle contracture, muscle spasms, myositis, non-cardiac chest pain, pain, pain in extremity and polyarthritis

§ Grouped terms: asthenia, fatigue and malaise

¶ Grouped terms: edema, face edema, localized edema, edema peripheral, peripheral swelling, periorbital edema, scrotal edema and swelling face

Grouped terms: colitis, mouth hemorrhage, mouth ulceration, mucosal inflammation, oropharyngeal pain, proctalgia, stomatitis, tongue discomfort and tongue ulceration

Ⓟ Grouped terms: acute respiratory failure, dyspnea, hypoxia and respiratory failure

β Grouped terms: dermatitis acneiform, dermatitis bullous, dermatitis exfoliative, erythema, rash, rash maculo-papular, rash papular, rosacea and skin ulcer

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%).

*Grouped terms: cardiac failure (cardiac failure, cardiac failure congestive, cardiomegaly, cardiomyopathy, chronic left ventricular failure, and ejection fraction decreased), hypersensitivity (anaphylactic reaction, angioedema, dermatitis allergic, drug hypersensitivity, erythema multiforme, hypersensitivity, and urticaria), pancreatitis (amylase increased, lipase increased, pancreatitis, pancreatitis acute), pericarditis/myocarditis (myocarditis, pericardial hemorrhage, pericardial rub, and pericarditis).

Selected post-baseline laboratory values that were observed in patients with relapsed or refractory AML are shown in Table 4.

Table 4: Shifts to Grade 3-4 Laboratory Abnormalities in Patients with Relapsed or Refractory AML by Pre-selected High Intensity and Low Intensity

Chemotherapy in the First 30 Days of the ADMIRAL Trial

	Pre-selected High Intensity Chemotherapy Subgroup		Pre-selected Low Intensity Chemotherapy Subgroup	
	XOSPATA (120 mg daily)	Chemotherapy	XOSPATA (120 mg daily)	Chemotherapy
Alanine aminotransferase increased	7/149 (5%)	1/66 (2%)	7/95 (7%)	1/41 (2%)
Alkaline phosphatase increased	1/149 (1%)	0	0	0
Aspartate aminotransferase increased	8/149 (5%)	2/65 (3%)	5/95 (5%)	0
Calcium decreased	2/149 (1%)	3/65 (5%)	3/94 (3%)	0
Creatine kinase increased	1/149 (1%)	0	1/95 (1%)	0
Phosphatase decreased	4/144 (3%)	6/65 (9%)	4/93 (4%)	3/38 (8%)
Sodium decreased	7/148 (5%)	5/65 (8%)	6/93 (6%)	2/41 (5%)
Triglycerides increased	1/146 (1%)	0	2/94 (2%)	0

7 DRUG INTERACTIONS

7.1 Effect of Other Drugs on XOSPATA

Combined P-gp and Strong CYP3A Inducers

Concomitant use of XOSPATA with a combined P-gp and strong CYP3A inducer decreases gilteritinib exposure which may decrease XOSPATA efficacy [see *Clinical Pharmacology (12.3)*]. 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 gilteritinib exposure [see *Clinical Pharmacology (12.3)*]. 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 [see *Dosage and Administration (2.3)*].

7.2 Effect of XOSPATA on Other Drugs

Drugs that Target 5HT_{2B} Receptor or Sigma Nonspecific Receptor

Concomitant use of gilteritinib may reduce the effects of drugs that target the 5HT_{2B}

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 [see *Clinical Pharmacology (12.3)*].

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 [see *Clinical Pharmacology (12.3)*].

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.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on findings from animal studies (see *Data*) and its mechanism of action, XOSPATA can cause fetal harm when administered to a pregnant woman [see *Clinical Pharmacology (12.1)*].

There are no available data on XOSPATA use in pregnant women to inform a drug-associated risk of adverse developmental outcomes. In animal reproduction studies, administration of gilteritinib to pregnant rats during organogenesis caused adverse developmental outcomes including embryo-fetal lethality, suppressed fetal growth, and teratogenicity at maternal exposures (AUC_{24}) approximately 0.4 times the AUC_{24} in patients receiving the recommended dose (see *Data*). Advise pregnant women of the potential risk to a fetus.

Adverse outcomes in pregnancy occur regardless of the health of the mother or the use of medications. The background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2%-4% and 15%-20%, respectively.

Data

Animal Data

In an embryo-fetal development study in rats, pregnant animals received oral doses of gilteritinib of 0, 0.3, 3, 10, and 30 mg/kg/day during the period of organogenesis. Maternal findings at 30 mg/kg/day (resulting in exposures approximately 0.4 times the AUC_{24} in patients receiving the recommended dose) included decreased body weight and food consumption. Administration of gilteritinib at the dose of 30 mg/kg/day also resulted in embryo-fetal death (postimplantation loss), decreased fetal body and placental weight, and decreased numbers of ossified sternbrae and sacral and caudal vertebrae, and increased incidence of fetal gross external (anasarca, local edema, exencephaly, cleft lip, cleft palate, short tail, and umbilical hernia), visceral

(microphthalmia; atrial and/or ventricular defects; and malformed/absent kidney, and malpositioned adrenal, and ovary), and skeletal (sternoschisis, absent rib, fused rib, fused cervical arch, misaligned cervical vertebra, and absent thoracic vertebra) abnormalities.

Single oral administration of [¹⁴C] gilteritinib to pregnant rats resulted in transfer of radioactivity to the fetus similar to that observed in maternal plasma on day 14 of gestation. In addition, distribution profiles of radioactivity in most maternal tissues and the fetus on day 18 of gestation were similar to that on day 14 of gestation.

8.2 Lactation

Risk Summary

There are no data on the presence of gilteritinib and/or its metabolites in human milk, the effects on the breastfed child, or the effects on milk production. Following administration of radiolabeled gilteritinib to lactating rats, milk concentrations of radioactivity were higher than radioactivity in maternal plasma at 4 and 24 hours post-dose. In animal studies, gilteritinib and/or its metabolite(s) were distributed to the tissues in infant rats via the milk. Because of the potential for serious adverse reactions in a breastfed child, advise a lactating woman not to breastfeed during treatment with XOSPATA and for 2 months after the last dose.

8.3 Females and Males of Reproductive Potential

XOSPATA can cause fetal harm when administered to a pregnant woman [see *Use in Specific Populations (8.1)*].

Pregnancy testing

Pregnancy testing is recommended for females of reproductive potential within seven days prior to initiating XOSPATA treatment [see *Use in Specific Populations (8.1)*].

Contraception

Females

Advise females of reproductive potential to use effective contraception during treatment and for 6 months after the last dose of XOSPATA.

Males

Advise males of reproductive potential to use effective contraception during treatment and for 4 months after the last dose of XOSPATA.

8.4 Pediatric Use

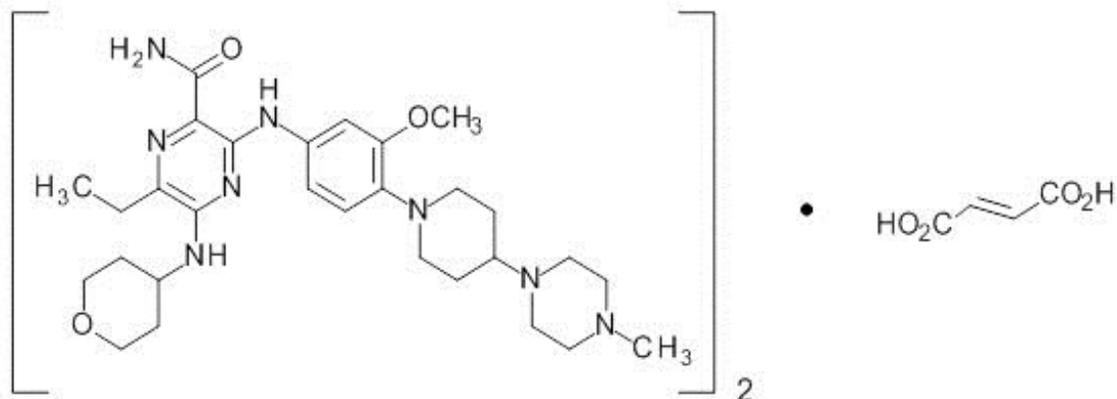
Safety and effectiveness in pediatric patients have not been established.

8.5 Geriatric Use

Of the 319 patients in clinical studies of XOSPATA, 43% were age 65 years or older, and 13% were 75 years or older. No overall differences in effectiveness or safety were observed between patients age 65 years or older and younger patients.

11 DESCRIPTION

Gilteritinib is a kinase inhibitor. The chemical name is 2-Pyrazinecarboxamide, 6-ethyl-3-[[3-methoxy-4-[4-(4-methyl-1-piperazinyl)-1-piperidinyl] phenyl] amino]-5-[(tetrahydro-2H-pyran-4-yl) amino]-, (2E)-2-butenedioate (2:1). The molecular weight is 1221.50 and the molecular formula is $(C_{29}H_{44}N_8O_3)_2 \cdot C_4H_4O_4$. The structural formula is:



Gilteritinib fumarate is a light yellow to yellow powder or crystals that is sparingly soluble in water and very slightly soluble in anhydrous ethanol.

XOSPATA (gilteritinib) is provided as a tablet for oral administration. Each tablet contains 40 mg of gilteritinib active ingredient as free base (corresponding to 44.2 mg gilteritinib fumarate). The inactive ingredients are ferric oxide, hydroxypropyl cellulose, hypromellose, low-substituted hydroxypropyl cellulose, mannitol, magnesium stearate, polyethylene glycol, talc, and titanium dioxide.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Gilteritinib is a small molecule that inhibits multiple receptor tyrosine kinases, including FMS-like tyrosine kinase 3 (FLT3). Gilteritinib demonstrated the ability to inhibit FLT3 receptor signaling and proliferation in cells exogenously expressing FLT3 including FLT3-ITD, tyrosine kinase domain mutations (TKD) FLT3-D835Y and FLT3-ITD-D835Y, and it induced apoptosis in leukemic cells expressing FLT3-ITD.

12.2 Pharmacodynamics

In patients with relapsed or refractory AML administered gilteritinib 120 mg, substantial (>90%) inhibition of FLT3 phosphorylation was rapid (within 24 hours after first dose) and sustained, as characterized by an *ex vivo* plasma inhibitory activity (PIA) assay.

Cardiac Electrophysiology

The effect of XOSPATA 120 mg once a day on the QTc interval has been evaluated in patients, which showed an absence of large mean increases (i.e., 20 msec) in the QTc interval.

Of 317 patients with a post-baseline QTc measurement on treatment with gilteritinib at

120 mg in clinical trials, 4 patients (1.3%) experienced a QTcF >500 msec. Additionally, across all doses 2.3% of patients with relapse/refractory AML had a maximum post-baseline QTcF interval >500 msec [see *Warnings and Precautions (5.3)*].

12.3 Pharmacokinetics

The following pharmacokinetic parameters were observed following administration of gilteritinib 120 mg once daily, unless otherwise specified.

Gilteritinib exposure (C_{\max} and AUC_{24}) increases proportionally with once daily doses ranging from 20 mg to 450 mg (0.17 to 3.75 times the recommended dosage) in patients with relapsed or refractory AML. Gilteritinib mean (\pm SD) steady-state C_{\max} is 374 ng/mL (\pm 190) and AUC_{24} is 6943 ng•hr/mL (\pm 3221). Steady-state plasma levels are reached within 15 days of dosing with an approximate 10-fold accumulation.

Absorption

The time to maximum gilteritinib concentration (t_{\max}) observed is approximately between 4 and 6 hours post dose in the fasted state.

Effect of Food

In healthy adults administered a single gilteritinib 40 mg dose (0.3 times the recommended dosage), gilteritinib C_{\max} decreased by 26% and AUC decreased by less than 10% when co-administered with a high-fat meal (approximately 800 to 1,000 total calories with 500 to 600 fat calories, 250 carbohydrate calories, 150 protein calories) compared to a fasted state. Median t_{\max} was delayed 2 hours when gilteritinib was administered with a high-fat meal.

Distribution

The population mean (%CV) estimates of apparent central and peripheral volume of distribution were 1092 L (9.22%) and 1100 L (4.99%), respectively, which may indicate extensive tissue distribution. *In vivo*, gilteritinib is approximately 94% bound to human plasma proteins. *In vitro*, gilteritinib is primarily bound to human serum albumin.

Elimination

The estimated half-life of gilteritinib is 113 hours, and the estimated apparent clearance is 14.85 L/h.

Metabolism

Gilteritinib is primarily metabolized via CYP3A4 *in vitro*. At steady state, the primary metabolites in humans include M17 (formed via N-dealkylation and oxidation), M16 and M10 (both formed via N-dealkylation). None of these 3 metabolites exceeded 10% of overall parent exposure.

Excretion

After a single radiolabeled dose, gilteritinib is excreted in feces with 64.5% of the total administered dose recovered in feces. Of the total radiolabeled dose of gilteritinib, 16.4% was recovered in urine as unchanged drug and metabolites.

Specific Populations

Age (20-87 years), sex, race, mild (Child-Pugh Class A) or moderate (Child-Pugh Class B) hepatic impairment and mild (creatinine clearance (CLCr) 50-80 mL/min) or moderate

(CLCr 30-50 mL/min) renal impairment do not have clinically meaningful effects on the pharmacokinetics of gilteritinib.

The effect of severe hepatic (Child-Pugh Class C) or severe renal impairment (CLCr \leq 29 mL/min) on gilteritinib pharmacokinetics is unknown.

Drug Interaction Studies

Clinical Studies

Combined P-gp and Strong CYP3A Inducers:

Gilteritinib C_{max} decreased approximately 30% and AUC decreased approximately 70% when co-administered with rifampin (a combined P-gp and strong CYP3A inducer).

Strong CYP3A Inhibitors:

Gilteritinib C_{max} increased approximately 20% and AUC increased approximately 120% when co-administered with itraconazole (a strong CYP3A inhibitor).

Moderate CYP3A Inhibitors:

Gilteritinib C_{max} increased approximately 16% and AUC increased approximately 40% when co-administered with fluconazole (a moderate CYP3A inhibitor).

CYP3A Substrates:

Midazolam (a CYP3A substrate) C_{max} and AUC increased approximately 10% when co-administered with gilteritinib.

MATE1 Substrates:

Cephalexin (a MATE1 substrate) C_{max} and AUC decreased by less than 10% when co-administered with gilteritinib.

In Vitro Studies

Gilteritinib inhibits human 5HT_{2B} receptor or sigma nonspecific receptors, which may reduce the effects of drugs that target these receptors such as escitalopram, fluoxetine and sertraline.

Gilteritinib is a substrate of P-gp and BCRP. Gilteritinib inhibits BCRP, P-gp and OCT1 at clinically relevant concentrations.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity studies have not been performed with gilteritinib.

Gilteritinib was not mutagenic in a bacterial mutagenesis (Ames) assay and was not clastogenic in a chromosome aberration test assay in Chinese hamster lung cells. Gilteritinib was positive for the induction of micronuclei in mouse bone marrow cells from 65 mg/kg (195 mg/m²) the mid dose tested (approximately 2.6 times the recommended human dose of 120 mg).

The effect of XOSPATA on human fertility is unknown. Administration of 10 mg/kg/day gilteritinib in the 4-week study in dogs (12 days of dosing) resulted in degeneration and

necrosis of germ cells and spermatid giant cell formation in the testis as well as single cell necrosis of the epididymal duct epithelia of the epididymal head.

13.2 Animal Toxicology and/or Pharmacology

In the 13-week oral repeated dose toxicity studies in rats and dogs, target organs of toxicity included the eye and kidney.

14 CLINICAL STUDIES

14.1 Relapsed or Refractory Acute Myeloid Leukemia

The efficacy of XOSPATA was assessed in the ADMIRAL Trial (NCT02421939), which included adult patients with relapsed or refractory AML having a FLT3 ITD, D835, or I836 mutation by the LeukoStrat[®] CDx FLT3 Mutation Assay. XOSPATA was given orally at a starting dose of 120 mg daily until unacceptable toxicity or lack of clinical benefit.

First Interim Analysis

The efficacy of XOSPATA was established on the basis of the rate of complete remission (CR)/CR with partial hematological recovery (CRh), the duration of CR/CRh (DOR), and the rate of conversion from transfusion dependence to transfusion independence at the first interim analysis in the ADMIRAL trial (n=138). The median follow-up was 4.6 months (95% CI: 2.8, 15.8). Fourteen patients were still in remission at the time of the first interim DOR analysis. The efficacy results are shown in Table 5. For patients who achieved a CR/CRh, the median time to first response was 3.6 months (range, 0.9 to 9.6 months). The CR/CRh rate was 29 of 126 in patients with FLT3-ITD or FLT3-ITD/TKD and 0 of 12 in patients with FLT3-TKD only.

Among the 106 patients who were dependent on red blood cell (RBC) and/or platelet transfusions at baseline, 33 (31.1%) became independent of RBC and platelet transfusions during any 56-day post-baseline period. For the 32 patients who were independent of both RBC and platelet transfusions at baseline, 17 (53.1%) remained transfusion-independent during any 56-day post-baseline period.

Table 5: Efficacy Results in Patients with Relapsed or Refractory AML Treated with XOSPATA in the First Interim Analysis (ADMIRAL Trial)

	XOSPATA N=138
Remission Rate	
CR*/CRh[†] n/N (%)	29/138 (21)
95% CI [‡]	14.5, 28.8
Median DOR [§] (months)	4.6
Range (months)	0.1 to 15.8 [¶]
CR* n/N (%)	16/138 (11.6)
95% CI [‡]	6.8, 18.1
Median DOR [§] (months)	8.6
Range (months)	1 to 13.8
CRh[†] n/N (%)	13/138 (9.4)
95% CI [‡]	5.1, 15.6

Median DOR [§] (months)	2.9
Range (months)	0.1 to 15.8 [¶]

CI: confidence interval; NE: not estimable; NR: not reached; Only responses prior to HSCT were included in response rate.

* CR was defined as an absolute neutrophil count $\geq 1.0 \times 10^9/L$, platelets $\geq 100 \times 10^9/L$, normal marrow differential with $< 5\%$ blasts, must have been red blood cells, platelet transfusion independent and no evidence of extramedullary leukemia.

† CRh was defined as marrow blasts $< 5\%$, partial hematologic recovery absolute neutrophil count $\geq 0.5 \times 10^9/L$ and platelets $\geq 50 \times 10^9/L$, no evidence of extramedullary leukemia and could not have been classified as CR.

‡ The 95% CI rate was calculated using the exact method based on binomial distribution.

§ 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. Deaths were counted as events.

¶ Response was ongoing.

Final Analysis

The final analysis of the ADMIRAL trial included 371 adult patients randomized 2:1 to receive XOSPATA 120 mg once daily (n=247) over continuous 28-day cycles or a prespecified chemotherapy regimen (n=124). Randomization was stratified by response to first-line AML therapy and prespecified chemotherapy. The prespecified chemotherapy regimens included high intensity combinations (MEC and FLAG-IDA) and low intensity regimens (LDAC and AZA).

The demographic and disease characteristics of the randomized patients are shown in Table 6.

Table 6: Baseline Demographic and Disease Characteristics in Patients with Relapsed or Refractory AML in the Final Analysis (ADMIRAL Trial)

Demographic and Disease Characteristics	Xospata (120 mg daily) N=247	Chemotherapy N=124
Demographics		
Median Age (Years) (Range)	62 (20, 84)	62 (19, 85)
Age Categories, n (%)		
<65 years	141 (57)	75 (60)
≥ 65 years	106 (43)	49 (40)
Sex, n (%)		
Male	116 (47)	54 (44)
Female	131 (53)	70 (57)
Race, n (%)		
White	145 (59)	75 (60)
Asian	69 (28)	33 (27)
Black or African American	14 (6)	7 (6)
Native Hawaiian or Other Pacific Islander	1 (0.4)	0
Other	5 (2)	1 (0.8)
Unknown/Missing	13 (5)	8 (6)
Baseline ECOG PS, n (%)		
0-1	206 (83)	105 (85)

≥2	41 (17)	19 (15)
Disease Characteristics		
Untreated relapse AML, n (%)	151 (61)	74 (60)
Primary refractory AML, n (%)	96 (39)	49 (40)
Refractory relapse AML, n (%)	0	1 (0.8)
Number of Relapses, n (%)		
0	96 (39)	49 (40)
1	149 (60)	74 (60)
2 or more	2 (0.8)	1 (0.8)
Median number of relapses (Range)	1 (0, 2)	1 (0, 2)
Transfusion Dependent at Baseline, n (%)*	197 (80)	97 (89)
FLT3 Mutation Status, n (%)		
ITD alone	215 (87)	113 (91)
TKD alone	21 (9)	10 (8)
ITD and TKD	7 (3)	0
Prior Use of FLT3 Inhibitor[†], n (%)		
No	215 (87)	110 (89)
Yes	32 (13)	14 (11)
Prespecified Chemotherapy		
High Intensity	149 (60)	75 (60)
MEC [‡]	-	33 (27)
FLAG-IDA [§]	-	42 (34)
Low Intensity	98 (40)	49 (40)
LDAC [¶]	-	17 (14)
AZA [#]	-	32 (26)

AML: acute myeloid leukemia; FLT3: FMS-related tyrosine kinase 3; ITD: internal tandem duplication; TKD: D835/I836 tyrosine kinase domain point mutation; ECOG PS: Eastern Cooperative Oncology Group performance status

- * Patients were defined as transfusion dependent at baseline if they were dosed and received any red blood cell or platelet transfusions within the 56-day baseline period.
- † Prior use of FLT3 inhibitor is defined as “Yes” if patients received prior AML therapy of midostaurin, sorafenib or quizartinib; otherwise, prior use of FLT3 inhibitor was assigned as “No.”
- ‡ MEC: mitoxantrone 8 mg/m², etoposide 100 mg/m² and cytarabine 1000 mg/m² once daily by IV for 5 days
- § FLAG-IDA: granulocyte colony-stimulating factor 300 mcg/m² once daily by SC days 1 to 5, fludarabine 30 mg/m² once daily by IV days 2 through 6, cytarabine 2000 mg/m² once daily by IV for days 2 through 6, idarubicin 10 mg/m² once daily by IV days 2 through 4
- ¶ LDAC: cytarabine 20 mg twice daily by subcutaneous (SC) or intravenous (IV) for 10 days
- # AZA: azacitidine 75 mg/m² once daily by SC or IV for 7 days

The final analysis included an assessment of OS, measured from the date of randomization until death by any cause. At the time of analysis, median follow-up was 17.8 months (range, 14.9 to 19.1). Patients randomized to the XOSPATA arm had significantly longer survival compared to the chemotherapy arm (HR 0.64; 95% CI: 0.49 – 0.83; 1-sided p-value: 0.0004). Figure 1 and Table 7 show the results of the OS analysis.

Exploratory subgroup analyses demonstrated that the hazard ratio for survival was 0.66 (95% CI: 0.47 – 0.93) for patients in the high intensity chemotherapy stratum and 0.56 (95% CI: 0.38 – 0.84) for patients in the low intensity chemotherapy stratum. The CR rates are shown in Table 7. For patients on XOSPATA and chemotherapy arms, the CR rates were 15.4% (95% CI: 10% – 22.3%) and 16% (95% CI: 8.6% – 26.3%), respectively, for patients in the high intensity chemotherapy stratum, and 12.2% (95% CI: 6.5% – 20.4%) and 2% (95% CI 0.1% – 10.9%), respectively, for patients in the low intensity chemotherapy stratum.

Table 7: OS and CR* in Patients with Relapsed or Refractory AML in the Final Analysis (ADMIRAL Trial)

	XOSPATA N=247	Chemotherapy N=124
Overall Survival		
Deaths, n (%)	171 (69.2%)	90 (72.6%)
Median in months (95% CI)	9.3 (7.7, 10.7)	5.6 (4.7, 7.3)
Hazard Ratio (95% CI)	0.64 (0.49, 0.83)	
p-value (1-sided)	0.0004	
Complete Remission		
CR, n (%)	35 (14.2%)	13 (10.5%)
(95% CI [†])	(10.1, 19.2)	(5.7, 17.3)
Median DOR [‡] (range) (months)	14.8 (0.6 to 23.1+)	1.8 (<0.1+ to 1.8)

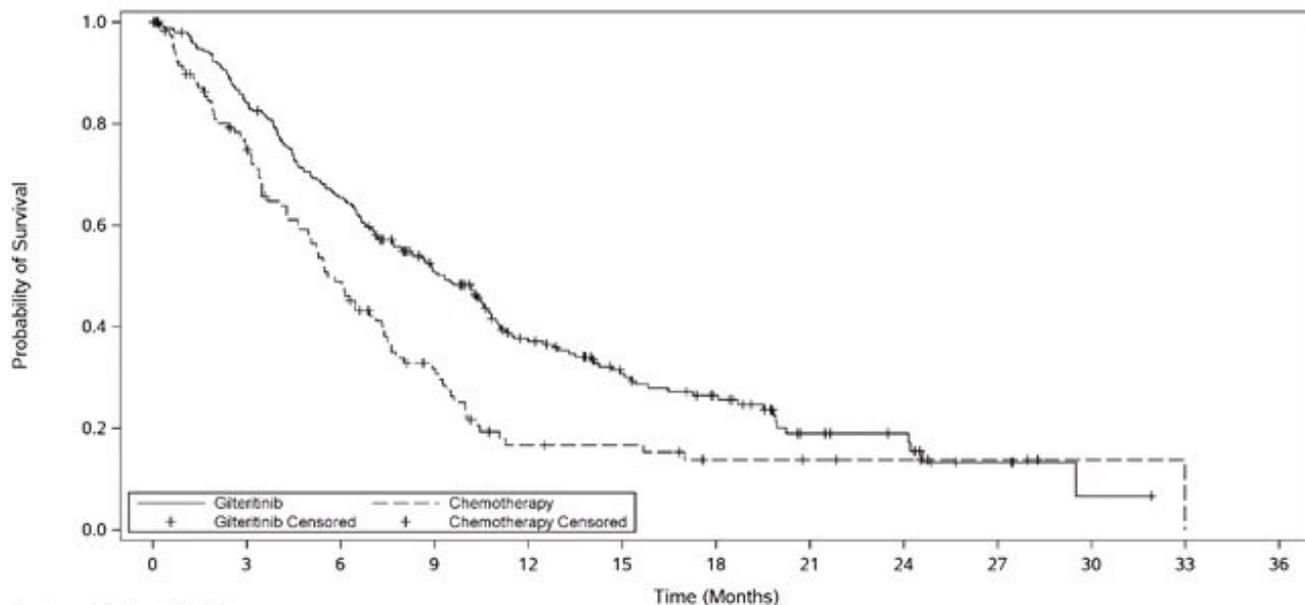
CI: confidence interval; Only responses prior to HSCT were included in response rate.

* CR was defined as an absolute neutrophil count $\geq 1.0 \times 10^9/L$, platelets $\geq 100 \times 10^9/L$, normal marrow differential with <5% blasts, must have been red blood cells, platelet transfusion independent and no evidence of extramedullary leukemia.

† The 95% CI rate was calculated using the exact method based on binomial distribution.

‡ DOR was defined as the time from the date of first remission until the date of a documented relapse.

Figure 1: Kaplan-Meier Plot of Overall Survival in ADMIRAL Trial



Number of Subjects At Risk		0	3	6	9	12	15	18	21	24	27	30	33	36
Gilteritinib	+	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

In the final analysis, the CR/CRh rate in the gilteritinib arm was 22.6% (55/243) and the DOR was 7.4 months (range, <0.1+ to 23.1+). For patients who achieved a CR/CRh, the median time to first response was 2 months (range, 0.9 to 9.6 months). The CR/CRh rate was 49 of 215 in patients with FLT3-ITD only, 3 of 7 in patients with FLT3-ITD/TKD and 3 of 21 in patients with FLT3-TKD only.

Among the 197 patients who were dependent on red blood cell (RBC) and/or platelet transfusions at baseline, 68 (34.5%) became independent of RBC and platelet transfusions during any 56-day post-baseline period. For the 49 patients who were independent of both RBC and platelet transfusions at baseline, 29 (59.2%) remained transfusion-independent during any 56-day post-baseline period

16 HOW SUPPLIED/STORAGE AND HANDLING

How Supplied

XOSPATA (gilteritinib) 40 mg tablets are supplied as light yellow, round-shaped, film-coated tablets debossed with the Astellas logo and '235' on the same side. XOSPATA tablets are available in the following package size:

- Bottles of 90 tablets with Child Resistant Closure (NDC 0469-1425-90)

Storage

Store XOSPATA tablets at 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C to 30°C (59°F to 86°F) [See USP Controlled Room Temperature]. Keep in original container until dispensed. Protect from light, moisture and humidity.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide).

Differentiation Syndrome

Advise patients of the risks of developing differentiation syndrome as early as 1 day after the start of therapy and during the first 3 months on treatment. Ask patients to immediately report any symptoms suggestive of differentiation syndrome, such as fever, cough or difficulty breathing, rash, low blood pressure, rapid weight gain, swelling of their arms or legs, or decreased urinary output, to their healthcare provider for further evaluation [see *Boxed Warning and Warnings and Precautions (5.1)*].

Posterior Reversible Encephalopathy Syndrome

Advise patients of the risk of developing posterior reversible encephalopathy syndrome (PRES). Ask patients to immediately report any symptoms suggestive of PRES, such as seizure and altered mental status, to their healthcare provider for further evaluation [see *Warnings and Precautions (5.2)*].

Prolonged QT Interval

Advise patients to consult their healthcare provider immediately if they feel faint, lose consciousness, or have signs or symptoms suggestive of arrhythmia. Advise patients with a history of hypokalemia or hypomagnesemia of the importance of monitoring their electrolytes [see *Warnings and Precautions (5.3)*].

Pancreatitis

Advise patients of the risk of pancreatitis and to contact their healthcare provider for signs or symptoms of pancreatitis, which include severe and persistent stomach pain, with or without nausea and vomiting [see *Warnings and Precautions (5.4)*].

Use of Contraceptives

- Advise female patients with reproductive potential to use effective contraceptive methods while receiving XOSPATA and for 6 months after completion of treatment.
- Advise patients to notify their healthcare provider immediately in the event of a pregnancy or if pregnancy is suspected during XOSPATA treatment.
- 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 [see *Use in Specific Populations (8.3)*].

Lactation

Advise women not to breastfeed during treatment with XOSPATA for 2 months after the last dose [see *Use in Specific Populations (8.2)*].

Dosing Instructions

- Advise patients not to break, crush or chew the tablets but to swallow them whole with a cup of water.
- Instruct patients that, if they miss a dose of XOSPATA, to take it as soon as possible on the same day, and at least 12 hours prior to the next scheduled dose, and return to the normal schedule the following day. Instruct patients to not take 2 doses within 12 hours [see *Dosage and Administration (2.2)*].

Distributed by:

Astellas Pharma US, Inc.
Northbrook, Illinois 60062

XOSPATA is a registered trademark of Astellas Pharma Inc.
LeukoStrat is a registered trademark of Invivoscribe, Inc.
©2021 Astellas Pharma US, Inc.
312959-GLT-USA

MEDICATION GUIDE
XOSPATA® (Zoh spah' tah)
(gilteritinib)
tablets

What is the most important information I should know about XOSPATA?
XOSPATA may cause serious side effects, including:

- **Differentiation Syndrome.** Differentiation syndrome is a condition that affects your blood cells and may be life-threatening or lead to death if not treated. Differentiation syndrome can happen as early as 1 day after starting XOSPATA and during the first 3 months of treatment. Call your healthcare provider or go to the nearest hospital emergency room right away if you develop any of the following symptoms of differentiation syndrome while taking XOSPATA:
 - o fever
 - o cough
 - o trouble breathing
 - o rash
 - o dizziness or lightheadedness
 - o rapid weight gain
 - o swelling of your arms or legs
 - o decreased urination

If you develop any of these symptoms of differentiation syndrome, your healthcare provider may treat you with a corticosteroid medicine and may monitor you in the hospital.

See “**What are the possible side effects of XOSPATA?**” for more information about side effects.

What is XOSPATA?

XOSPATA is a prescription medicine used to treat adults with acute myeloid leukemia (AML) who have a FMS-like tyrosine kinase 3 (FLT3) mutation:

- when the disease has come back, or
- has not improved after previous treatment(s).

Your healthcare provider will perform a test to make sure that XOSPATA is right for you. It is not known if XOSPATA is safe and effective in children.

Do not take XOSPATA if you are allergic to gilteritinib or any of the ingredients in XOSPATA. See the end of this Medication Guide for a complete list of ingredients in XOSPATA.

Before taking XOSPATA, tell your healthcare provider about all of your medical conditions, including if you:

- have any heart problems, including a condition called long QT syndrome.
- have problems with abnormal electrolytes such as sodium, potassium, or magnesium levels.

- are pregnant or plan to become pregnant. XOSPATA can cause harm to your unborn baby. Tell your healthcare provider right away if you become pregnant or think you may be pregnant during treatment with XOSPATA.
 - o If you are able to become pregnant, your healthcare provider may perform a pregnancy test 7 days before you start treatment with XOSPATA.
 - o **Females** who are able to become pregnant should use effective birth control (contraception) during treatment with XOSPATA and for 6 months after the last dose of XOSPATA.
 - o **Males** who have female partners that are able to become pregnant should use effective birth control (contraception) during treatment with XOSPATA and for 4 months after the last dose of XOSPATA.
- are breastfeeding or plan to breastfeed. It is not known if XOSPATA passes into your breast milk. Do not breastfeed during treatment with XOSPATA and for 2 months after the last dose of XOSPATA.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements. XOSPATA may affect the way other medicines work and other medicines may affect how XOSPATA works.

How should I take XOSPATA?

- Take XOSPATA exactly as your healthcare provider tells you to. Do not change your dose or stop taking XOSPATA without talking to your healthcare provider.
- Take XOSPATA 1 time a day at about the same time each day.
- Swallow XOSPATA tablets whole. Do not break, crush, or chew the tablet.
- XOSPATA can be taken with or without food.

If you miss a dose of XOSPATA, or did not take it at the usual time, take your dose as soon as possible and at least 12 hours before your next dose. Return to your normal schedule the following day. Do not take 2 doses of XOSPATA within 12 hours.

What are the possible side effects of XOSPATA?

XOSPATA may cause serious side effects, including:

- **See “What is the most important information I should know about XOSPATA?”**
- **Posterior Reversible Encephalopathy Syndrome (PRES).** If you take XOSPATA, you may be at risk of developing a condition involving the brain called PRES. Tell your healthcare provider right away if you have a seizure or quickly worsening symptoms such as headache, decreased alertness, confusion, reduced eyesight, blurred vision, or other visual problems. Your healthcare provider will do a test to check for PRES. Your healthcare provider will stop XOSPATA if you develop PRES.
- **Changes in the electrical activity of your heart called QTc prolongation. QTc prolongation can cause irregular heartbeats that can be life-threatening.** Your healthcare provider will check the electrical activity of your heart with a test called an electrocardiogram (ECG) before you start taking XOSPATA and during your treatment with XOSPATA. Tell your healthcare provider right away if you feel dizzy, lightheaded, or faint. The risk of QT prolongation is higher in people with low blood magnesium or low blood potassium levels. Your

healthcare provider will do blood tests to check your potassium and magnesium levels before and during your treatment with XOSPATA.

- **Inflammation of the pancreas (pancreatitis).** Tell your healthcare provider right away if you have severe stomach (abdomen) pain that does not go away. This pain may happen with or without nausea and vomiting.

The most common side effects of XOSPATA include:

- o changes in liver function tests
- o joint or muscle pain
- o tiredness
- o fever
- o pain or sores in mouth or throat
- o swelling of arms or legs
- o rash
- o diarrhea
- o shortness of breath
- o nausea
- o cough
- o constipation
- o eye problems
- o headache
- o dizziness
- o low blood pressure
- o vomiting
- o decreased urination

Your healthcare provider may tell you to decrease your dose, temporarily stop, or completely stop taking XOSPATA if you develop certain side effects during treatment with XOSPATA.

These are not all of the possible side effects of XOSPATA.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store XOSPATA?

- XOSPATA comes in a child resistant package.
- Store XOSPATA at room temperature between 68°F to 77°F (20°C to 25°C).
- Keep XOSPATA in the original container to protect it from light, moisture, and humidity.
- **Keep XOSPATA and all medicines out of the reach of children.**

General information about the safe and effective use of XOSPATA.

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use XOSPATA for a condition for which it was not prescribed. Do not give XOSPATA to other people, even if they have the same symptoms that you have. It may harm them. You can ask your pharmacist or healthcare provider for information about XOSPATA that is written for healthcare professionals.

What are the ingredients in XOSPATA?

Active ingredient: gilteritinib

Inactive ingredients: ferric oxide, hydroxypropyl cellulose, hypromellose, low-substituted hydroxypropyl cellulose, mannitol, magnesium stearate, polyethylene glycol, talc, and titanium dioxide.

Distributed by: Astellas Pharma US, Inc., Northbrook, Illinois 60062

XOSPATA is a registered trademark of Astellas Pharma Inc.

©2021 Astellas Pharma US, Inc.

For more information about XOSPATA, call 1-800-727-7003, or visit www.XOSPATA.com.

312959-GLT-USA

PACKAGE/LABEL PRINCIPAL DISPLAY PANEL - 40 mg Tablet Bottle Carton



NDC 0469-1425-90

XOSPATA®
(gilteritinib) tablets
40 mg

Do not break, crush or chew tablets.

90 tablets

Rx only

XOSPATA

gilteritinib tablet

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	Item Code (Source)	NDC:0469-1425
Route of Administration	ORAL		

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
GILTERITINIB FUMARATE (UNII: 5RZZ0Z1GJT) (GILTERITINIB - UNII:66D92MGC8M)	GILTERITINIB	40 mg

Inactive Ingredients

Ingredient Name	Strength
MANNITOL (UNII: 3OWL53L36A)	
HYDROXYPROPYL CELLULOSE, UNSPECIFIED (UNII: 9XZ8H6N6OH)	
LOW-SUBSTITUTED HYDROXYPROPYL CELLULOSE, UNSPECIFIED (UNII: 2165RE0K14)	
MAGNESIUM STEARATE (UNII: 70097M6I30)	
HYPROMELLOSE, UNSPECIFIED (UNII: 3NXW29V3WO)	
TALC (UNII: 7SEV7J4R1U)	
POLYETHYLENE GLYCOL, UNSPECIFIED (UNII: 3WJQ0SDW1A)	
TITANIUM DIOXIDE (UNII: 15FIX9V2JP)	
FERRIC OXIDE RED (UNII: 1K09F3G675)	

Product Characteristics

Color	YELLOW (Light yellow)	Score	no score
Shape	ROUND	Size	7mm
Flavor		Imprint Code	Logo;235
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:0469-1425-90	1 in 1 CARTON	11/29/2018	
1		90 in 1 BOTTLE; Type 0: Not a Combination Product		
2	NDC:0469-1425-21	1 in 1 CARTON	04/30/2022	
2		21 in 1 BOTTLE; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA	NDA211349	11/29/2018	

Labeler - Astellas Pharma US, Inc. (605764828)

Establishment

Name	Address	ID/FEI	Business Operations
J. Knipper and Company, Inc.		080159814	PACK(0469-1425) , LABEL(0469-1425)

Revised: 1/2022

Astellas Pharma US, Inc.