Presentation: XOSPATA 40 mg film-coated tablets. **Composition**: Each film-coated tablet contains 40 mg gilteritinib (as fumarate). **Indication(s)**: XOSPATA is indicated as monotherapy for the treatment of adult patients who have relapsed or refractory acute myeloid leukaemia (AML) with a FLT3 mutation (see "Posology and method of administration). **Posology and Method of Administration**: Treatment with XOSPATA should be initiated and supervised by a physician experienced in the use of anti-cancer therapies. 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) (see Table 1). Posology: The recommended starting dose is 120 mg gilteritinib (three 40 mg tablets) once daily. Blood chemistries, including creatine phosphokinase, should be assessed prior to initiation of treatment, on day 15 and monthly for the duration of treatment. An electrocardiogram (ECG) should be performed before initiation of gilteritinib treatment, on day 8 and 15 of cycle 1 and prior to the start of the next three subsequent months of treatment (see "Warnings and Precautions" and "Undesirable Effects"). Treatment should continue until the patient is no longer clinically benefiting from XOSPATA or until unacceptable toxicity occurs. Response may be delayed; therefore, continuation of 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 CRc) after 4 weeks of treatment, the dose can be increased to 200 mg (five 40 mg tablets) once daily, if tolerated or clinically warranted. Dose modifications.

Table 1. XOSPATA dose interruption, reduction and discontinuation recommendations in patients with relapsed or refractory AML

Criteria	XOSPATA dosing
Symptoms of differentiation syndrome	• If differentiation syndrome is suspected, administer corticosteroids and initiate hemodynamic monitoring (see "Warnings and Precautions"). • 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.
Symptoms of posterior reversible encephalopathy syndrome	• Discontinue gilteritinib.
QTc interval >500 msec	• Interrupt gilteritinib. • Resume gilteritinib at a reduced dose (80 mg or 120 mg[b]) 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 cycle 1	• Confirm with ECG on day 9. • If confirmed, consider dose reduction to 80 mg or 120 mg[b].
Symptoms of pancreatitis	• Interrupt gilteritinib until pancreatitis is resolved. • Resume treatment with gilteritinib 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 serious, 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. Composite complete remission (CRc) is defined as the remission rate of all CR, CRp [achieved CR except for incomplete platelet recovery (<100 x 10^9/L)] and CRi (achieved all criteria for CR except for incomplete haematological recovery with residual neutropenia <1 x 10^9/L with or without complete platelet recovery). XOSPATA should be administered at about the same time each day. If a dose is missed or not taken at the usual time, the 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 is required in patients ≥65 years of age. *Hepatic impairment*: No dose adjustment is required for patients with mild (Child-Pugh Class A) or moderate (Child-Pugh Class B) hepatic impairment. XOSPATA is not recommended for use in patients with severe (Child-Pugh Class C) hepatic impairment, as safety and efficacy have not been evaluated in this population. *Renal impairment*: No dose adjustment is necessary in patients with mild or moderate renal impairment. There is no clinical experience in patients with severe renal impairment. *Paediatric population*: The safety and efficacy of XOSPATA in children aged below 18 years has not yet been established. No data are available. Due to in vitro binding to $5HT_{2B}$ (see "Interactions"), there is a potential impact on cardiac development in patients less than 6 months of age. Method of administration: XOSPATA is for oral use. The tablets can be taken with or without food. They should be swallowed whole with water and should not be broken or crushed. **Contraindications**: Hypersensitivity to the active substance or to any of the excipients. **Warnings and Precautions**: Differentiation syndrome: Gilteritinib has been associated with differentiation syndrome (see "Undesirable Effects"). Differentiation syndrome is associated with rapid proliferation and differentiation of myeloid cells and may be life-threatening or fatal if not treated. Symptoms and clinical findings of differentiation syndrome include fever, dyspnoea, pleural effusion, pericardial effusion, pulmonary oedema, hypotension, rapid weight gain, peripheral oedema, rash, and renal dysfunction. If differentiation syndrome is suspected, corticosteroid therapy should be initiated along with hemodynamic monitoring until symptom resolution. If severe signs and/or symptoms persist for more than 48 hours after initiation of corticosteroids, XOSPATA should be interrupted until signs and symptoms are no longer severe (see "Posology and Method of Administration" and "Undesirable Effects"). Corticosteroids can be tapered after resolution of symptoms and should be administered for a minimum of 3 days. Symptoms of differentiation syndrome may recur with premature discontinuation of corticosteroid treatment. Posterior reversible encephalopathy syndrome: There have been reports of posterior reversible encephalopathy syndrome (PRES) in patients receiving XOSPATA (see "Undesirable Effects"). PRES is a rare, reversible, neurological disorder which can present with rapidly evolving symptoms including seizure, headache, confusion, visual and neurological disturbances, with or without associated hypertension and altered mental status. If PRES is suspected, it should be confirmed by brain imaging, preferably magnetic resonance imaging (MRI). Discontinuation of XOSPATA in patients who develop PRES is recommended (see "Posology and Method of Administration" and "Undesirable Effects"). Prolonged QT interval: Gilteritinib has been associated with prolonged cardiac ventricular repolarisation (QT Interval) (see "Undesirable Effects"). QT prolongation can be observed in the first three months of treatment with gilteritinib. Therefore, electrocardiogram (ECG) should be performed prior to initiation of treatment, on day 8 and 15 of cycle 1, and prior to the start of the next three subsequent months of treatment. Caution is warranted in patients with relevant cardiac history. Hypokalaemia or hypomagnesaemia may increase the QT prolongation risk. Hypokalaemia or hypomagnesaemia should therefore be corrected prior to and during XOSPATA treatment. XOSPATA should be interrupted in patients who have a QTcF >500 msec (see "Posology and Method of Administration"). The decision to re-introduce gilteritinib treatment after an event of QT prolongation should be based on a 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. In clinical studies, 12 patients had QTcF >500 msec. Three patients interrupted and reinitiated treatment without recurrence of QT prolongation. 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 (see "Posology and Method of Administration"). Interactions: Co-administration of CYP3A/P-gp inducers may lead to decreased gilteritinib exposure and consequently a risk for lack of efficacy. Therefore, concomitant use of gilteritinib with strong CYP3A4/P-gp inducers should be avoided (see "Interactions"). Caution is required when concomitantly prescribing gilteritinib with medicinal products that are strong inhibitors of CYP3A and/or P-gp (such as, but not limited to, voriconazole, itraconazole, posaconazole and clarithromycin) because they can increase gilteritinib exposure. Alternative medicinal products that do not strongly inhibit CYP3A and/or P-gp activity should be considered. In situations where satisfactory therapeutic alternatives do not exist, patients should be closely monitored for toxicities during administration of gilteritinib (see "Interactions"). Gilteritinib may reduce the effects of medicinal products that target $5HT_{2B}$ receptor or sigma nonspecific receptors. Therefore, concomitant use of gilteritinib with these products should be avoided unless use is considered essential for the care of the patient (see "Interactions"). Embryofoetal toxicity and contraception: Pregnant women should be informed of the potential risk to a foetus (see "Fertility, pregnancy and lactation"). Females of reproductive potential should be advised to have a pregnancy test within seven days prior to starting treatment with XOSPATA and to use effective contraception during treatment with XOSPATA and for at least 6 months after stopping treatment. Women using hormonal contraceptives should add a barrier method of contraception. Males with female partners of reproductive potential should be advised to use effective contraception during treatment and for at least 4 months after the last dose of XOSPATA. **Interactions**: Gilteritinib is primarily metabolised by CYP3A enzymes, which can be induced or inhibited by a number of concomitant medicinal products. Effects of other medicinal products on XOSPATA: CYP3A/P-gp Inducers: Concomitant use of XOSPATA with strong CYP3A/P-gp inducers (e.g., phenytoin, rifampin and St. John's Wort) should be avoided because they can decrease gilteritinib plasma concentrations. In healthy subjects, co-administration of rifampicin (600 mg), a strong CYP3A/P-gp inducer, to steady state with a single 20 mg dose of gilteritinib decreased gilteritinib mean C_{max} by 27% and mean AUC_{inf} by 70%, respectively, compared to subjects administered a single dose of gilteritinib alone (see "Warnings and Precautions "). CYP3A and/or P-gp inhibitors: Strong inhibitors of CYP3A and/orP-gp (e.g., voriconazole, itraconazole, posaconazole, clarithromycin, erythromycin, captopril, carvedilol, ritonavir, azithromycin) can increase gilteritinib plasma concentrations. A single, 10 mg dose of gilteritinib co-administered with itraconazole (200 mg once daily for 28 days), a strong CYP3A and/or P-gp inhibitor, to healthy subjects resulted in an approximate 20% increase in mean C_{max} and 2.2-fold increase in mean AUC_{inf} relative to subjects administered a single dose of gilteritinib alone. Gilteritinib exposure increased approximately 1.5-fold in patients with relapsed or refractory AML when co-administered with a strong CYP3A and/orP-gp inhibitor (see "Warnings and Precautions ").Gilteritinib as an inhibitor or inducer Gilteritinib is not an inhibitor or inducer of CYP3A4 or and inhibitor of MATE1 in vivo. The pharmacokinetics of midazolam (a sensitive CYP3A4 substrate) were not significantly (C_{max} and AUC increased approximately 10%) affected after once-daily administration of gilteritinib (300 mg) for 15 days in patients with FLT3-mutated relapsed or refractory AML. Additionally, the pharmacokinetics of cephalexin (a sensitive MATE1 substrate) were not significantly (C_{max} and AUC decreased by less than 10%) affected after once daily administration of gilteritinib (200 mg) for 15 days in patients with FLT3-mutated relapsed or refractory AML. Effects of XOSPATA on other medicinal products: $5HT_{2B}$ receptor or sigma nonspecific receptor Based on in vitro data, gilteritinib may reduce the effects of medicinal products that target $5HT_{2B}$ receptor or sigma nonspecific receptor (e.g., escitalopram, fluoxetine, sertraline). Avoid concomitant use of these medicinal products with XOSPATA unless use is considered essential for the care of the patient. **Fertility, pregnancy and lactation**: Women of childbearing potential / Contraception in males and females Pregnancy testing is recommended for females of reproductive potential seven days prior to initiating XOSPATA treatment. Women of childbearing potential are 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, and therefore women using hormonal contraceptives should add a barrier method of contraception. Males of reproductive potential should be advised to use effective contraception during treatment and for at least 4 months after the last dose of XOSPATA (see "Warnings and Precautions "). 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 have shown that gilteritinib caused suppressed foetal growth, embryo-foetal deaths and teratogenicity. XOSPATA is not recommended during pregnancy and in women of childbearing potential not using effective contraception. Breast-feeding It is unknown whether gilteritinib or its metabolites are excreted in human milk. Available animal data have shown excretion of gilteritinib and its metabolites in the animal milk of lactating rats and distribution to the tissues in infant rats via the milk. A risk to the breast-fed children cannot be excluded. Breast-feeding should be discontinued during treatment with XOSPATA and for at least two months after the last dose. Fertility: There are no data on the effect of gilterinitib on human fertility. **Effects on ability to drive and use machines**: Gilteritinib has minor influence on the ability to drive and use machines. Dizziness has been reported in patients taking XOSPATA and should be considered when assessing a patient's ability to drive or use machines (see "Undesirable Effects"). **Undesirable Effects**: Summary of the safety profile: The safety of XOSPATA was evaluated in 319 patients with relapsed or refractory AML who have received at least one dose of 120 mg gilteritinib. The most frequent adverse reactions with gilteritinib were, blood creatine phosphokinase increased (93.4%), alanine aminotransferase (ALT) increased (82.1%), aspartate aminotransferase (AST) increased (80.6%), blood alkaline phosphatase increased (68.7%), , diarrhoea (35.1%), fatigue (30.4%), nausea (29.8%), constipation (28.2%), cough (28.2%), peripheral oedema (24.1%), dyspnea (24.1%), dizziness (20.4%), hypotension (17.2%), pain in extremity (14.7%), asthenia (13.8%), arthralgia (12.5%) and myalgia (12.5%). The most frequent serious adverse reactions were diarrhoea (4.7%), ALT increased (4.1%), dyspnea (3.4%), AST increased (3.1%) and hypotension (2.8%). Other clinically significant serious adverse reactions included differentiation syndrome (2.2%), electrocardiogram QT prolonged (0.9%) and posterior reversible encephalopathy syndrome (0.6%). Tabulated list of adverse reactions: Adverse reactions observed during clinical studies are listed below by frequency category. Frequency categories are defined as follows: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000); not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 2: 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
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.

Description of selected adverse reactions: *Differentiation syndrome*: Of 319 patients treated with XOSPATA in the clinical studies, 11 (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 clinical findings of differentiation syndrome in patients treated with XOSPATA included fever, dyspnoea, pleural effusion, pericardial effusion, pulmonary oedema, hypotension, rapid weight gain, peripheral oedema, rash, and renal dysfunction. Some cases had concomitant acute febrile neutrophilic dermatosis. Differentiation syndrome occurred as early as two days and up to 75 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. For recommendations in case of suspected differentiation syndrome see sections “Posology and Method of Administration” and “Warnings and Precautions”. PRES: Of the 319 patients treated with XOSPATA in the clinical studies, 0.6% experienced posterior reversible encephalopathy syndrome (PRES). PRES is a rare, reversible, neurological disorder, which can present with rapidly evolving symptoms including seizure, headache, confusion, visual and neurological disturbances, with or without associated hypertension. Symptoms have resolved after discontinuation of treatment (see “Posology and Method of Administration” and “Warnings and Precautions”). QT prolongation: Of the 317 patients treated with gilteritinib at 120 mg with a post-baseline QTC value in clinical studies, 4 patients (1%) experienced a QTcF >500 msec. Additionally, across all doses, 12 patients (2.3%) with relapsed/refractory AML had a maximum post-baseline QTcF interval >500 msec (see “Posology and Method of Administration” and “Warnings and Precautions”). Reporting of suspected adverse reactions: Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system.

For more detailed information, please refer to the full Prescribing Information as available with Astellas Medical Representative. Legal category: POM; **MA Holder**: Astellas Pharma Europe B.V., Sylviusweg 62, 2333 BE Leiden, NL. **Further information available upon request from**: Astellas Pharma International B.V. Technical and Scientific Office, , Riyadh, Kingdom of Saudi Arabia. **Version**: 1.0. In case of any suspected adverse events or any safety information associated with XOSPATA, please report immediately to pharmacovigilance.ae@astellas.com; tel: +966112933024