Prescribing information: XOSPATA™ (gilteritinib) 40 mg film-coated tablets.

Presentation: xospata 40 mg film-coated tablets containing 40 mg gilteritinib (as fumarate). For the full list of excipients, see Summary of Product Characteristics (SPC) section 6.1. **Indications:** Gilteritinib is indicated as monotherapy for the treatment of adult patients who have relapsed or refractory acute myeloid leukaemia (AML) with a FLT3 mutation.

Posology and administration: Treatment with gilteritinib 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. The recommended starting dose is 120 mg gilteritinib (three 40 mg tablets) orally once daily, with or without food, swallowed whole with water and should not be broken or crushed. Gilteritinib 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. 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 SPC sections 4.4 and 4.8). Females of reproductive potential should be advised to have a pregnancy test within seven days prior to starting treatment with Xospata (see SPC sections 4.4 and 4.6). Treatment should continue until the patient is no longer clinically benefiting from gilteritinib 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 composite complete remission (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. Gilteritinib may be re-initiated in patients following haematopoietic stem cell transplantation (HSCT), Planned HSCT: Interrupt treatment 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. See SPC section 4.2 for full information on dosing modifications & use in special populations.

Contraindications: Hypersensitivity to the active substance or to any of the excipients listed in section 6.1 of the SPC.

Special warnings and precautions for use: Differentiation syndrome: Gilteritinib has been associated with differentiation syndrome (see SPC section 4.8). 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 haemodynamic monitoring until symptom resolution. If severe signs and/or symptoms persist for more than 48 hours after initiation of corticosteroids, gilteritinib should be interrupted until signs and symptoms are no longer severe (see SPC sections 4.2 and 4.8). 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. Resume gilteritinib at the same dose when signs and symptoms improve to Grade 2 or lower. Posterior reversible encephalopathy syndrome: There have been reports of posterior reversible encephalopathy syndrome (PRES) in patients receiving gilteritinib (see SPC section 4.8). 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 gilteritinib in patients who develop PRES is recommended (see SPC sections 4.2 and 4.8). Prolonged QT interval: Gilteritinib has been associated with prolonged cardiac ventricular repolarisation (QT interval), (see SPC sections 4.8 and 5.1). QT prolongation can be observed in the first three months of treatment with gilteritinib. Therefore, 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 gilteritinib treatment. Gilteritinib should be interrupted in patients who have

a QTcF >500 msec (see SPC section 4.2).The decision to re-introduce gilteritinib treatment after an event of QT prolongation should be based on careful consideration of benefits and risks. Resume gilteritinib at a reduced dose (from 120 mg to 80 mg or from 200 mg to 120 mg) when QTcF interval returns to within 30 msec of baseline or ≤480 msec. Patients with QTcF interval increase by >30 msec on day 8 of cycle 1 should have a further ECG on day 9; if QTcF increase is confirmed gilteritinib dose should be reduced to 80 mg. If gilteritinib 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 re-initiated 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. Gilteritinib should be interrupted and can be resumed at a reduced dose (reduced from 120 mg to 80 mg or from 200 mg to 120 mg) when the signs and symptoms of pancreatitis have resolved (see SPC section 4.2). Toxicity: If the patient experiences other Grade 3 or higher toxicity considered related to treatment, interrupt treatment until the toxicity resolves or improves to Grade 1. If deemed clinically appropriate gilteritinib can be resumed at a reduced dose (reduced from 120 mg to 80 mg or from 200 mg to 120 mg). See SPC section 4.2 for full information on dosing modifications. Severe renal impairment: Gilteritinib exposure may be increased in patients with severe renal impairment or end stage renal disease. Patients should be closely monitored for toxicities and QT prolongation during administration of gilteritinib (see SPC section 5.2). 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 SPC section 4.5). Caution is required when concomitantly prescribing gilteritinib with medicinal products that are strong inhibitors of CYP3A,P-gp and/or breast cancer resistant protein (BCRP) because they can increase gilteritinib exposure. Alternative medicinal products that do not strongly inhibit CYP3A, P-gp and/or BCRP 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 SPC section 4.5). 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 SPC section 4.5). Embryofoetal toxicity and contraception: Pregnant women should be informed of the potential risk to a foetus (see SPC sections 4.6 and 5.3). Females of reproductive potential should be advised to have a pregnancy test within seven days prior to starting treatment with gilteritinib and to use effective contraception during treatment with gilteritinib 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 gilteritinib.
Interactions: Gilteritinib is primarily metabolised by CYP3A enzymes, which can be induced or inhibited by a number of concomitant medicinal products. See Special Warnings and Precautions for Use section above for further information on this and the effects of gilteritinib on products that target $5HT_{2B}$ receptor or sigma nonspecific receptors. *Gilteritinib as an inhibitor or inducer:* gilteritinib is not an inhibitor or inducer of CYP3A4 or an inhibitor of MATE1 *in vivo*. Gilteritinib is an inhibitor of P-gp, BCRP and OCT1 (organic cation transporter 1) *in vitro*. As no clinical data is available, it cannot be excluded that gilteritinib could inhibit these transporters at a therapeutic dose. Caution is advised during co-administration of gilteritinib with substrates of P-gp (e.g., digoxin, dabigatran etexilate), BCRP (e.g., mitoxantrone, methotrexate, rosuvastatin) and OCT1 (e.g., metformin).
Fertility, pregnancy and lactation: 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 (see SPC section 5.3). Gilteritinib is not recommended during pregnancy and in women of childbearing potential not using effective contraception. See Special Warnings and Precautions for Use section above for information on pregnancy testing and contraception. Breastfeeding: 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 (see SPC section 5.3). A risk to breast-fed children cannot be excluded. Breastfeeding should be discontinued during treatment with gilteritinib 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 gilteritinib and should be considered when assessing a patient's ability to drive or use machines (see SPC section 4.8).

Undesirable effects: Summary of the safety profile: The safety of gilteritinib 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 alanine aminotransferase (ALT) increased (82.1%), aspartate aminotransferase (AST) increased (80.6%), blood alkaline phosphatase increased (68.7%), blood creatine phosphokinase increased (53.9%), 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 acute kidney injury (6.6%), 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%).

List of adverse reactions: Adverse reactions observed during clinical studies are listed below by MedDRA system organ class and 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.

Immune system disorders:
Anaphylactic reaction (common); All Grades 1.3%, Grades ≥3 1.3%

Nervous system disorders:
Dizziness (very common); All Grades 20.4%, Grades ≥3 0.3%,
Posterior reversible encephalopathy syndrome (uncommon); All Grades 0.6%, Grades ≥3 0.6%

Cardiac disorders:
Electrocardiogram QT prolonged (common); All Grades 8.8%, Grades ≥3 2.5%,
Pericardial effusion (common); All Grades 4.1%, Grades ≥3 0.9%,
Pericarditis (common); All Grades 1.6%, Grades ≥3 0%,
Cardiac failure (common); All Grades 1.3%, Grades ≥3 1.3%

Vascular disorders:
Hypotension (very common); All Grades 17.2%, Grades ≥3 7.2%

Respiratory, thoracic and mediastinal disorders:
Cough (very common); All Grades 28.2%, Grades ≥3 0.3%,
Dyspnoea (very common); All Grades 24.1%, Grades ≥3 4.4%,
Differentiation syndrome (common); All Grades 3.4%, Grades ≥3 2.2%

Gastrointestinal disorders:
Diarrhoea (very common); All Grades 35.1%, Grades ≥3 4.1%,
Nausea (very common); All Grades 29.8%, Grades ≥3 1.9% ,
Constipation (very common); All Grades 28.2%, Grades ≥3 0.6%

Hepatobiliary disorders:
Alanine aminotransferase increased*(very common); All Grades 82.1%, Grades ≥3 12.9%,
Aspartate aminotransferase increased*(very common); All Grades 80.6%, Grades ≥3 10.3%

Musculoskeletal and connective tissue disorders:
Blood creatine phosphokinase increased*(very common); All Grades 53.9%, Grades ≥3 6.3%,
Blood alkaline phosphatase increased*(very common); All Grades 68.7%, Grades ≥3 1.6%,
Pain in extremity (very common); All Grades 14.7%, Grades ≥3 0.6%,
Arthralgia (very common); All Grades 12.5%, Grades ≥3 1.3%,
Myalgia (very common); All Grades 12.5%, Grades ≥3 0.3%,
Musculoskeletal pain(common); All Grades 4.1%, Grades ≥3 0.3%

Renal and urinary disorders:
Acute kidney injury (common); All Grades 6.6%, Grades ≥3 2.2%

General disorders and administration site conditions:
Fatigue (very common); All Grades 30.4%, Grades ≥3 3.1%,
Peripheral oedema (very common); All Grades 24.1%, Grades ≥3 0.3%,
Asthenia (very common); All Grades 13.8%, Grades ≥3 2.5%,
Malaise (common); All Grades 4.4%, Grades ≥3 0%

* Frequency is based on central laboratory values.

Description of selected adverse reactions: *Differentiation syndrome*: Of 319 patients treated with gilteritinib 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 gilteritinib 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 one day and up to 82 days after gilteritinib 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 gilteritinib. For recommendations in case of suspected differentiation syndrome see SPC sections 4.2 and 4.4. *PRES*: Of the 319 patients treated with gilteritinib in the clinical studies, 0.6% experienced 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 SPC sections 4.2 and 4.4). *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 SPC sections 4.2, 4.4 and 5.1). Prescribers should consult the full summary of product characteristics in relation to other adverse events.

Overdose: There is no known specific antidote for gilteritinib. In the event of an overdose, treatment should be stopped. Patients must be closely monitored for signs or symptoms of adverse reactions, and appropriate symptomatic and supportive treatment initiated, taking into consideration the long half-life estimated at 113 hours.

Cost (excluding VAT): XOSPATA 40 mg film-coated tablets x 84: £14,188.00 **Legal classification:** POM. **Marketing authorisation number:** PLGB 00166/0425. **Marketing authorisation holder:** Astellas Pharma Ltd., 300 Dashwood Lang Road, Bourne Business Park, Addlestone, United Kingdom, KT15 2NX. **Date of preparation of prescribing information:** September 2024. **Document number:** MAT-GB-XOS-2024-00138. **Further information available from:** Astellas Pharma Ltd., Medical Information: 0800 783 5018. For full prescribing information, please see the SPC which may be found at:
www.medicines.org.uk;

<u>Great Britain</u>

Adverse events should be reported. Reporting forms and information can be found at www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store. Adverse events should also be reported to Astellas Pharma Ltd. on 0800 783 5018.

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