Abbreviated prescribing information of Xospata

Abbreviated prescribing information of Xospata® 40 mg film-coated tablets

Version: 001

Composition:

Gilteritinib

Indications:

Monotherapy for the treatment of adult patients who have relapsed or refractory acute myeloid leukaemia (AML) with a FLT3 mutation.

Dosage:

120 mg gilteritinib (three 40 mg tablets) once daily.

Administration:

Swallowed whole with water and should not be broken or crushed, can be taken with or without food.

Contraindications:

Hypersensitivity to the active substance or to any of the excipients.

Special warnings and precautions for use:

Differentiation syndrome

Gilteritinib has been associated with 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 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.

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. 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.

Prolonged QT interval

Gilteritinib has been associated with prolonged cardiac ventricular repolarisation (QT Interval). 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.

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.

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.

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) (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, 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.

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.

Embryofoetal toxicity and contraception

Pregnant women should be informed of the potential risk to a foetus. 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.

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 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%), dyspnoea (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%), dyspnoea (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.

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 one 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.

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.

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.

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.

Full prescribing information is available upon request.