XOSPATA™ (GILTERITINIB)

Public Risk Management Plan (RMP) Summary

The Risk Management Plan (RMP) is a comprehensive document submitted as part of the application dossier for market approval of a medicine. The RMP summary contains information on the medicine's safety profile and explains the measures that are taken in order to further investigate and follow the risks as well as to prevent or minimise them. The RMP summary of Xospata is a concise document and does not claim to be exhaustive. As the RMP is an international document, the summary might differ from the "Arzneimittelinformation / Information sur le médicament" approved and published in Switzerland, e.g. by mentioning risks occurring in populations or indications not included in the Swiss authorization. Please note that the reference document which is valid and relevant for the effective and safe use of Xospata in Switzerland is the "Arzneimittelinformation/ Information sur le médicament" (see www.swissmedic.ch) approved and authorized by Swissmedic. Astellas Pharma AG is fully responsible for the accuracy and correctness of the content of the published summary RMP of Xospata.

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Astellas Pharma AG
Richtiring 28, CH-8304 Wallisellen
Tel. +41 (0)44 832 40 00, Fax +41 (0)44 832 40 99
office.ch@astellas.com, www.astellas.ch

VI SUMMARY OF THE RISK MANAGEMENT PLAN

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Summary of risk management plan for XOSPATA (gilteritinib)

This is a summary of the risk management plan (RMP) for XOSPATA. The RMP details important risks of XOSPATA, how these risks can be minimized, and how more information will be obtained about XOSPATA's risks and uncertainties (missing information).

XOSPATA's local label gives essential information to healthcare professionals and patients on how XOSPATA should be used.

This summary of the RMP for XOSPATA should be read in the context of all this information and its plain-language summary.

Important new concerns or changes to the current ones will be included in updates of XOSPATA's RMP.

I. The medicine and what it is used for

XOSPATA is authorized as monotherapy for treatment of adult patients who have relapsed or refractory acute myeloid leukemia (AML) with an FMS-like tyrosine kinase (FLT3) mutation (see the local label for the full indication). It contains gilteritinib as the active substance and it is available as a film-coated 40 mg tablet.

II. Risks associated with the medicine and activities to minimize or further characterize the risks

Important risks of XOSPATA, together with measures to minimize such risks and the proposed studies for learning more about XOSPATA's risks, are outlined below.

Measures to minimize the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the local label addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorized pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimize its risks.

Together, these measures constitute *routine risk minimization* measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analyzed, including periodic safety update report (PSUR) assessment, so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

If important information that may affect the safe use of XOSPATA is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of XOSPATA are risks that need special risk management activities to further investigate or minimize the risk, so that the medicinal product can be safely taken. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of XOSPATA. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g., on the long-term use of the medicine).

List of important risks and missing information	
Important identified risks	• Posterior reversible encephalopathy syndrome (PRES) • Differentiation syndrome • QT prolongation
Important potential risks	• Pancreatitis • Embryo-fetal lethality, suppressed fetal growth, and teratogenicity
Missing information	• Safety in patients with renal impairment

II.B Summary of important risks

Important identified risk: Posterior reversible encephalopathy syndrome (PRES)	
Evidence for linking the risk to the medicine	PRES is a rare neurological disorder that can present with rapidly evolving symptoms including seizure, headache, confusion, blindness, and other visual and neurological disturbances, with or without associated hypertension. A diagnosis of PRES requires confirmation by brain imaging, preferably MRI. In clinical trials, there have been uncommon reports of PRES with gilteritinib with symptoms including seizure and altered mental status. Symptoms have resolved after discontinuation of gilteritinib. Early recognition of PRES may mitigate secondary complications that can lead to morbidity/mortality. Discontinuation of gilteritinib in patients who develop PRES is recommended.
Risk factors and risk groups	In general, there appears to be a predominance of female PRES cases to male cases; the syndrome occurs across many age groups (pediatric, adult, and elderly) [Fugate et al, 2010; Li et al, 2012; Li et al, 2013]. PRES has been linked to a number of medical conditions including hypertensive encephalopathy, renal disease, systemic inflammatory syndrome, autoimmune disease, and vasculitis [Le & Loghin, 2014]. PRES has also been linked to medications including chemotherapies (e.g. anthracyclines and alkylating agents), monoclonal antibodies, and immunosuppressant drugs [Le & Loghin, 2014]. PRES has also been associated with use of several multikinase inhibitors (e.g., sunitinib, sorafenib) [Costa et al, 2014; Foerster et al, 2013].

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Important identified risk: Posterior reversible encephalopathy syndrome (PRES)	
Risk minimization measures	Routine risk communication: • local label; Routine risk minimization activities recommending specific clinical measures to address the risk: • Recommendation to discontinue gilteritinib in patients who develop PRES is provided in local label.
Additional pharmacovigilance activities	None

MRI: magnetic resonance imaging PRES: posterior reversible encephalopathy syndrome.

Important identified risk: Differentiation Syndrome	
Evidence for linking the risk to the medicine	Differentiation syndrome is associated with rapid proliferation and differentiation of myeloid cells and may be life-threatening or fatal if not treated. Of the 319 patients treated with gilteritinib in the clinical trials, 3% experienced differentiation syndrome. Symptoms of differentiation syndrome in patients treated with gilteritinib 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 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.
Risk factors and risk groups	Patients treated with chemotherapeutic agents and targeted therapies that induce myeloid differentiation are at risk for developing differentiation syndrome as a rare treatment associated complication.
Risk minimization measures	Routine risk communication: • local label Routine risk minimization activities recommending specific clinical measures to address the risk: • Recommendation for monitoring is provided in local label; • Recommendation for treatment interruption of gilteritinib is provided in local label. Additional risk minimization measures: • Patient Alert Card
Additional pharmacovigilance activities	None

AML: acute myeloid leukemia.

Important identified risk: QT prolongation	
Evidence for linking the risk to the medicine	Gilteritinib has been associated with prolonged cardiac ventricular repolarization (QT interval). A concentration-related increase in change from baseline of QTcF was observed across gilteritinib doses ranging from 20 to 450 mg. The effect of gilteritinib 120 mg once a day on QTc has been evaluated in patients, which showed an absence of large mean increases (i.e., 20 msec) in the QTc interval. Of 319 patients treated with gilteritinib at 120 mg tested in clinical trials, 4 patients (1.3%) experienced a QTcF > 500 msec. Additionally, across all doses, 2.3% of relapse/refractory subjects had a maximum post baseline QTcF interval > 500 msec. In clinical trials, there have been reports of QT prolongation with gilteritinib, occurring in approximately 7% of patients treated with gilteritinib (36/496 patients). Another approximately 7% (36/496 patients) experienced related events such as syncope, cardiac arrest, ventricular tachycardia, ventricular arrhythmia, loss of consciousness, ventricular fibrillation, and sudden death. There were no patients that discontinued gilteritinib due to QT prolongation. The clinical trials excluded patients with baseline QTcF ≥ 450 msec, long QT syndrome, hypokalemia or hypomagnesemia, or significant cardiovascular disease. Monitoring for arrhythmias and early recognition of QT prolongation may mitigate the development of serious outcomes. Interruption and/or dose reduction of gilteritinib in patients who develop QT prolongation (QTcF > 500 msec) is recommended.
Risk factors and risk groups	Patients with pre-existing QTcF > 450 msec, long QT syndrome, electrolyte abnormalities (hypokalemia or hypomagnesemia), or those who are taking medications known to prolong the QT interval (e.g., anti-arrhythmic medicines, fluoroquinolones, triazole antifungals, and 5-HT3 [serotonin type 3] receptor antagonists) may be at a higher risk for QT prolongation. A concentration-related increase in changes from baseline for QTcF was observed across gilteritinib doses ranging from 20 to 450 mg. Therefore, strong inhibitors of CYP3A or P-gp, such as, antifungals (e.g., voriconazole, posaconazole), antibiotics (e.g., clarithromycin, azithromycin), angiotensin-converting enzyme inhibitors (e.g., captopril), antivirals (e.g., ritonavir), and beta blockers (e.g., carvedilol) may increase the risk of QTc interval prolongation because they can increase gilteritinib plasma concentrations.

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Risk minimization measures	Routine risk communication: • Description of QT prolongation is included in: o local label; Routine risk minimization activities recommending specific clinical measures to address the risk: • Recommendation for ECG monitoring is provided in local label; • Recommendation for treatment interruption of gilteritinib in patients with QTc > 500 msec with resumption at a reduced dose when QTc interval returns to baseline or ≤480 msec is provided in local label • Recommendation to correct hypokalemia or hypomagnesemia prior to and during gilteritinib administration is provided in local label, as hypokalemia or hypomagnesemia may increase QT prolongation.
Additional pharmacovigilance activities	None
CYP: cytochrome P450; ECG: electrocardiogram; P-gp: P-glycoprotein; QTc: QT interval corrected for heart rate; QTcF: QT interval corrected for heart rate using Fridericia's formula.	

Important potential risk: Pancreatitis	
Evidence for linking the risk to the medicine	Acute pancreatitis and pancreatitis have been observed in gilteritinib clinical trials; however, an association with gilteritinib has not been confirmed.
Risk factors and risk groups	Risk factors for pancreatitis in the general population include hyperlipidemia, diabetes, alcohol use, and cigarette smoking. In AML patients, pancreatitis can occur secondary to sepsis and infection.
Risk minimization measures	Routine risk communication: • local label; Routine risk minimization activities recommending specific clinical measures to address the risk: • Recommendation to evaluate and monitor patients who develop signs and symptoms suggestive of pancreatitis is provided in local label.

AML: acute myeloid leukemia.

Important potential risk: Embryo-fetal lethality, suppressed fetal growth, and teratogenicity	
Evidence for linking the risk to the medicine	Gilteritinib can cause fetal harm when administered to pregnant women. There are no data from the use of gilteritinib in pregnant women. Embryo-fetal development studies in rats with gilteritinib have shown suppressed fetal growth, embryo-fetal deaths, and teratogenicity.
Risk factors and risk groups	Persons at risk include female patients of child-bearing potential, as well as male patients with female partners who are of child-bearing potential.
Risk minimization measures	Routine risk communication: • local label; Routine risk minimization activities recommending specific clinical measures to address the risk: • Recommendation for females of childbearing potential to use contraception during treatment and for at least 6 months after the last dose of gilteritinib is provided in local label; • Recommendation for fertile men to use effective contraception during treatment and for at least 4 months after the last dose is provided in local label.

Missing Information: Safety in patients with renal impairment	
Risk minimization measures	• None
Additional pharmacovigilance activities	• None

II.C Postauthorization development plan

II.C.1 Studies which are conditions of the marketing authorization

There are no studies that are conditions of the marketing authorization or specific obligation of XOSPATA.

II.C.2 Other studies in postauthorization development plan

Not applicable