

XOSPATA™ ▼ (gilteritinib)

HCP Educational Information Brochure

This HCP Educational Information Brochure is an Additional Risk Minimisation Measure of the XOSPATA™ Risk Management Plan provided by Astellas Pharma International B.V. Israel

HCP – healthcare professional

▼ **This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reaction.**

For prescribing information, please refer to the XOSPATA™ physician leaflet provided with this brochure or please refer to the physician leaflet available in MOH site

Date of preparation: January 2021 XOS_2020_0021_IL

v.02: This Prescriber Brochure format and content have been updated and approved by the Ministry of Health on Feb 2021.



This HCP Educational Information Brochure aims to provide information about Differentiation Syndrome related to XOSPATA™, to minimise the risk associated with this safety concern.

Every healthcare professional must read and understand this HCP Educational tool before prescribing XOSPATA™.

Please refer to this brochure to support the health and safety of your patients and advise your patients to understand the risk of developing Differentiation Syndrome before using XOSPATA™.

Other adverse events associated with XOSPATA™ are listed in the physician leaflet provided with this brochure.

XOSPATA™	4
Indication	
Adverse reactions	
Important information on Differentiation Syndrome associated with XOSPATA™	
DIFFERENTIATION SYNDROME	5
Incidence of Differentiation Syndrome in AML patients treated with XOSPATA™	
Aetiology and pathogenesis	
Signs and symptoms	
Diagnosis	
Differential diagnosis	
Treatment	
PATIENT ALERT CARD.....	7
REPORTING OF SUSPECTED ADVERSE REACTIONS	7
CONTACT DETAILS	7
REFERENCES.....	8

XOSPATA™

XOSPATA™ (gilteritinib fumarate) is an FMS-like tyrosine kinase 3 (FLT3) and AXL inhibitor. XOSPATA™ inhibits FLT3 receptor signaling and proliferation in cells exogenously expressing FLT3 including FLT3 internal tandem duplication (FLT3-ITD), FLT3-D835Y and FLT3-ITD-D835Y, and induces apoptosis in leukaemic cells expressing FLT3-ITD.¹

INDICATION

XOSPATA™ is indicated as monotherapy for the treatment of adult patients who have relapsed or refractory acute myeloid leukaemia (AML) with a FLT3 mutation.¹

ADVERSE REACTIONS

319 patients have been treated with XOSPATA™ in the gilteritinib clinical development program. The most frequent serious adverse reactions were:¹

- Acute kidney injury (6.6%)
- Diarrhoea (4.7%)
- Alanine aminotransferase (ALT) increased (4.1%)
- Dyspnoea (3.4%)
- Aspartate aminotransferase (AST) increased (3.1%) and
- Hypotension (2.8%)

Other clinically significant serious adverse reactions included:¹

- Differentiation Syndrome (2.2%)
- Electrocardiogram QT prolonged (0.9%) and
- Posterior Reversible Encephalopathy Syndrome (0.6%)

IMPORTANT INFORMATION ON DIFFERENTIATION SYNDROME ASSOCIATED WITH XOSPATA™

Differentiation Syndrome may be life-threatening or fatal if not treated.¹ This HCP Educational Information Brochure provides information about Differentiation Syndrome related to XOSPATA™ to minimise the risk associated with this safety concern.

For prescribing information, please refer to the XOSPATA™ physician leaflet provided with this brochure or please refer to the physician leaflet available in MOH site.

DIFFERENTIATION SYNDROME

INCIDENCE OF DIFFERENTIATION SYNDROME IN AML PATIENTS TREATED WITH XOSPATA™

Of the 319 patients treated with XOSPATA™ in the clinical development program, 11 (3.4%) experienced Differentiation Syndrome (all grades). In 7 out of these 11 patients, Differentiation Syndrome was reported as Grade ≥ 3 .¹

AETIOLOGY AND PATHOGENESIS

Differentiation Syndrome develops in patients with acute promyelocytic leukaemia (APL) and other AML subtypes treated with agents that can affect differentiation, such as FLT3 inhibitors like gilteritinib.^{1,2}

The precise mechanism implicated in the pathogenesis of Differentiation Syndrome is not known, but it has been linked to the production of inflammatory cytokines released by rapid proliferation and differentiation of myeloid cells into neutrophils, causing a systemic inflammatory response and a capillary-leak syndrome.³ XOSPATA™ can induce differentiation of myeloblasts in patients with AML.⁴

Post-mortem studies in patients with APL showed leukaemic infiltration of lymph nodes, spleen, lung, liver, pleura, kidney, pericardium and skin.³

SIGNS AND SYMPTOMS

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.¹

Symptoms and clinical findings of Differentiation Syndrome in patients treated with XOSPATA™ included:¹

- Fever
- Dyspnoea
- Pleural effusion
- Pericardial effusion
- Peripheral Oedema
- Hypotension
- Rapid weight gain
- Peripheral oedema
- Rash
- Renal dysfunction
- Some cases had concomitant acute febrile neutrophilic dermatosis

Musculoskeletal pain, hyperbilirubinaemia and pulmonary haemorrhage were also reported as findings of Differentiation Syndrome in patients treated for APL.⁵

DIAGNOSIS

No single sign or symptom is considered sufficient to diagnose Differentiation Syndrome, and any possible alternative cause explaining the clinical features should be ruled out first.

The diagnosis of Differentiation Syndrome is mostly based on the presence of the above clinical and radiological criteria, and supported by the striking response to early therapy with intravenous corticosteroids.⁵

DIFFERENTIAL DIAGNOSIS

The differential diagnosis should always include lung infection, sepsis, thromboembolism and heart failure.⁶

TREATMENT

- The experience in the treatment of gilteritinib-related Differentiation Syndrome is very limited
- Corticosteroids (dexamethasone 10 mg IV every 12 hours or an equivalent dose of an alternative oral or IV corticosteroid) should be administered at the earliest clinical suspicion of Differentiation Syndrome, along with haemodynamic monitoring until improvement^{1,2}
- Gilteritinib should be interrupted if severe signs and/or symptoms persist for more than 48 hours after the initiation of corticosteroids¹
- Gilteritinib can be resumed at the same dose when signs and symptoms improve to Grade 2 or lower¹
- Corticosteroids can be tapered after resolution of symptoms and should be administered for a minimum of 3 days¹
- Symptoms of Differentiation Syndrome may recur with premature discontinuation of corticosteroid treatment¹
- Delayed administration of corticosteroids is associated with poor outcomes in APL Differentiation Syndrome^{5,6}

PATIENT ALERT CARD

Your patients will receive a Patient Alert Card in their XOSPATA™ package. This card will help them understand Differentiation Syndrome better. Please instruct your patients to:

- Fill the Patient Alert Card and carry it with them at all times
- Show the Patient Alert Card to any healthcare professional they might interact with for any medical treatment (including pharmacy), or at any visits to the hospital or clinic

Tell your patients to talk to you immediately or go to the nearest hospital emergency room if they develop fever, trouble breathing, rash, dizziness or lightheadedness, rapid weight gain, or swelling of arms or legs.

REPORTING OF SUSPECTED ADVERSE REACTIONS

Ensuring the safe use of XOSPATA™ is critical. Astellas's commitment and obligation is to collect and report suspected adverse reactions occurring during the use of XOSPATA™. Please report any suspected adverse reaction to Astellas Drug Safety. Any suspected adverse event should be reported to the Ministry of Health according to the National Regulation by using an online form <https://sideeffects.health.gov.il/>

Adverse events may also be reported to Astellas Pharma International B.V Pharmacovigilance.IL@astellas.com

CONTACT DETAILS

Astellas Pharma International B.V

21 St. Ha'Melacha, Rosh Ha Ayin, Israel, 4809157

www.astellas.com/il

Israel Affiliate Medical Information medinfo.il@astellas.com

REFERENCES

1. XOSPATA physician leaflet.
2. Sanz MA, Fenaux P, Tallman MS, Estey EH, Löwenberg B, Naoe T et al. Management of acute promyelocytic leukemia: updated recommendations from an expert panel of the European LeukemiaNet. *Blood* 2019;133(15):1630-1643.
3. Frankel SR, Eardley A, Lauwers G, Weiss M, Warrell RP Jr. The "Retinoic Acid Syndrome" in acute promyelocytic leukemia. *Ann Intern Med* 1992;117(4):292-296.
4. McMahan CM, Canaani J, Rea B, Sargent RL, Qualtieri JN, Watt CD et al. Gilteritinib induces differentiation in relapsed and refractory FLT3-mutated acute myeloid leukemia. *Blood Adv* 2019;3(10):1581-1585.
5. Montesinos P and Sanz MA. The Differentiation Syndrome in patients with acute promyelocytic leukemia: experience of the Pethema group and review of the literature. *Mediterr J Hematol Infect Dis* 2011;3(1): e2011059.
6. Cabral R, Caballero JC, Alonso S, Dávila J, Cabrero M, Caballero D et al. Late Differentiation Syndrome in acute promyelocytic leukemia: a challenging diagnosis. *Hematol Rep* 2014;6(4):5654.

▼ **This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions.**

For prescribing information, please refer to the XOSPATA™ physician leaflet provided with this brochure or please refer to the physician leaflet available in MOH site.

© 2020 Astellas Pharma Inc. All rights reserved.

XOSPATA™, Astellas, and the flying star logo are trademarks of Astellas Pharma Inc.