14.01.2021

רופא/ה רוקח/ת נכבד/ה,
ברצוננו להודיעך על עדכון בעלון לרופא ועלון לצרכן של

Xospata 40 mg, Film coated tablets

חומר פעיל:

Gilteritinib (As Fumarate) 40 mg

להלן עדכונים בעלון לרופא (טקסט מסומן ירוק משמעותו עדכון, טקסט מסומן בצהוב משמעותו החמרה):

Patient guide
The marketing of Xospata is subject to a risk management plan (RMP) including a Patient guide. The Patient guide, emphasizes important safety information that the patient should be aware of before and during treatment.
Please explain to the patient the need to review the card before starting treatment.

Prescriber guide
This product is marketed with prescriber providing important safety information. Please ensure you are familiar with this material as it contains important safety information.

[…]

3. PHARMACEUTICAL FORM

Film-coated tablet (tablet).

[…]

4.2 Posology and method of administration

[…]

In the absence of a response [(patient did not achieve a composite complete remission (CRc)] ~~CRc~~) after 4 weeks of treatment, the dose can be increased to 200 m[g (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 d~~Differentiation syndrome	• If differentiation syndrome is suspected, administer corticosteroids and initiate hemodynamic monitoring (see section 4.4). • 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~~ Posterior reversible encephalopathy syndrome	• Discontinue gilteritinib.
QTcF interval >500 msec	• Interrupt gilteritinib. • Resume gilteritinib at a reduced dose (80 mg or 120 mg[b]) when QTcF interval returns to within 30 msec of baseline or ≤ 480 msec.
QTcF 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 80mg. ~~mg or 120 mg[b].~~
~~Symptoms of p~~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 severe, ~~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 (see section 5.1 for definition of 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).

[…]

4.4 Special warnings and precautions for use

[…]

Prolonged QT interval

Gilteritinib has been associated with prolonged cardiac ventricular repolarisation (QT Interval) (see sections 4.8 and 5.1). QT prolongation can be observed in the first ~~two~~ three months of treatment with gilteritinib.

[…]

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) ~~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, P-gp and/or BCRP ~~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 section 4.5).

[…]

4.5 Interaction with other medicinal products and other forms of interaction

[…]

CYP3A, P-gp and/or BCRP ~~P-gp~~ inhibitors
Strong inhibitors of CYP3A, P-gp and/or BCRP ~~P-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, P-gp and~~/or~~ BCRP~~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, P-gp and/or BCRP~~P-gp~~ inhibitor (see section 4.4).

Effects of Xospata on other medicinal products
[…]

Gilteritinib is an inhibitor of P-gp, BCRP~~, OATP1B1~~ and OCT1 *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)~~, OATP1B1 (substrates)~~ and OCT1 (e.g., metformin).

~~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.

~~*P-gp substrates*~~
~~Gilteritinib is a P-gp inhibitor *in vitro*. As no clinical data are available on this interaction, it cannot be excluded that gilteritinib could inhibit intestinal P-gp after a therapeutic dose. Co-administration of oral P-gp substrates with narrow therapeutic range, such as digoxin or dabigatran etexilate should be used with caution and alternatives should be considered when possible. If use of P-gp substrates cannot be avoided, oral P-gp substrates should be taken at least 6 hours before Xospata to minimise the potential for an interaction in the gastrointestinal tract.~~

4.6 Fertility, pregnancy and lactation

[…]

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.

4.8 Undesirable effects

[…]

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%), 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%).

[…]

Description of selected adverse reactions

[…]
Differentiation syndrome occurred as early as ~~two~~ one day~~s~~ and up to ~~75~~ 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. For recommendations in case of suspected differentiation syndrome see sections 4.2 and 4.4.

[…]

4.9 Overdose

There is no known specific antidote for Xospata. In the event of an overdose, treatment with Xospata should be stopped. P~~p~~atients 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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antineoplastic agents, protein kinase inhibitors, ATC code: L01EX13~~L01XE54~~

Mechanism of action
Gilteritinib fumarate is a FLT3 and AXL inhibitor.
Gilteritinib inhibits FLT3 receptor signalling and proliferation in cells exogenously expressing FLT3 including FLT3-ITD, FLT3-D835Y, and FLT3-ITD-D835Y, and it ~~induced~~ induces apoptosis in leukemic cells expressing FLT3-ITD.

[…]

Clinical efficacy and safety
Relapsed or refractory AML
Efficacy and safety ~~was~~ were evaluated in the active-controlled, phase 3 study (2215-CL-0301)~~-~~.

[…]

- cytarabine 20 mg twice daily by subcutaneous injection (SC) or intravenous infusion (IV) for 10 days (days 1 through 10) (LoDAC)

[…]

5.2 Pharmacokinetic properties

Absorption
Following oral administration of gilteritinib, peak plasma concentrations are observed at a median t_{max} approximately between 4 and 6 hours in healthy volunteers and patients with relapsed or refractory AML. Gilteritinib undergoes first-order absorption with an estimated absorption rate (k_a) of 0.43 h^{-1} ~~h^{-1}~~ with a lag time of 0.34 hours based on population PK modelling.

[…]

Transporter drug-drug interactions
In vitro experiments demonstrated that gilteritinib is a ~~P-gp~~ substrate of P-gp and BCRP. Gilteritinib may potentially inhibit BCRP, ~~and~~ P-gp ~~in the small intestine~~ and, ~~in the liver~~ at clinically relevant concentrations (see section 4.5).

[…]

להלן העדכונים בעלון לצרכן (טקסט מסומן ירוק משמעותו עדכון, טקסט מסומן בצהוב משמעותו החמרה):

[...]

זוספטה 40 מ"ג
~~טבליות מצופות~~

[...]

כרטיס מידע למטופל:
כרטיס זה מכיל מידע בטיחותי חשוב שעליך לדעת לפני התחלת הטיפול בזוספטה ובמהלך הטיפול בזוספטה.
הכרטיס מכיל מידע המיועד הן למטופל והן לצוות הרפואי. הכרטיס מספק הדרכה למטופלים כיצד ניתן למזער את הסיכון לסינדרום ההתמיינות .
כמו כן, הכרטיס מכיל פרטים אישיים של המטופל ומידע לגבי התכשיר זוספטה לצוות הרפואי .
הצג כרטיס זה לכל איש צוות רפואי המעורב בטיפולך.

[...]

~~מהי זוספטה~~קבוצה תרפויטית
זוספטה משתייכת לקבוצה של תרופות לטיפול בסרטן הנקראות "מעכבי פרוטאין קינאז" (protein kinase inhibitors).

[...]

2. לפני השימוש בתרופה
[...]

- אם יש לך אחד מהתסמינים הבאים: חום, קושי לנשום, פריחה, סחרחורת או תחושת עילפון, עלייה מהירה במשקל, התנפחות של הידיים או הרגליים שלך. אלו עלולים להיות סימנים למצב הנקרא "תסמונת התמיינות" (differentiation syndrome) (ראה סעיף 4 – תופעות לוואי). תסמונת ההתמיינות יכולה להתרחש בכל זמן במהלך שלושת חודשי הטיפול הראשונים בזוספטה, החל מהיום הראשון לטיפול~~ימים לאחר תחילת הטיפול~~. אם

מתרחשת, הרופא שלך יבצע מעקב ועשוי לתת לך תרופה לטיפול במצבך. הרופא עשוי גם לעצור את הטיפול בזוספטה עד שהתסמינים פוחתים.

[...]
אינטראקציות\תגובות בין תרופתיות
[...]

- תרופות המשמשות לטיפול בבעיות לב כגון דיגוקסין;
- תרופות המשמשות למנוע קרישי דם כגון דביגאטרן אטקסילאט

[...]
3. **כיצד תשתמש בתרופה?**
[...]
אם נטלת בטעות מנה גדולה יותר מהמומלץ
אם נטלת יותר טבליות ממה שעליך לקחת, הפסק ליטול זוספטה וצור קשר עם הרופא שלך.
אם בטעות בלע ילד מן התרופה, צור מייד קשר עם רופא או גש לחדר מיון בבית חולים והבא את אריזת התרופה איתך.

[...]
4. **תופעות לוואי**
[...]
שכיחות (עלולות להשפיע על עד 1 מתוך 10 אנשים):
[...]
- דלקת בלב (פריקרדיטיס)
- אי-ספיקת לב

~~**לא שכיחות (עלולות להשפיע על עד 1 מתוך 100 אנשים):**~~
~~- דלקת בלב (פריקרדיטיס)~~
~~- אי-ספיקת לב~~
[...]
5. **איך לאחסן את התרופה?**
אין תנאי אחסון מיוחדים. מומלץ לשמור בטמפרטורת החדר.

[...]

בעל הרישום וכתובתו:
אסטלס פארמה אינטרנשיונל בי.וי.~~B.V.~~, רחוב המלאכה 21, ראש העין, 4809157.

העלונים לרופא ולצרכן נשלחו למאגר התרופות שבאתר משרד הבריאות www.health.gov.il לצורך העלאתם לאתר וניתן לקבלם מודפסים על ידי פניה לבעל הרישום אסטלס פארמה אינטרנשונל בי.וי., ת.ד. 11458, ראש העין, מספר טלפון: 03-7501166.

בברכה
גל פרידמן
רוקח ממונה