Medicines & Healthcare products Regulatory Agency

DRUG SAFETY UPDATE (DSU)

Fezolinetant▼(Veoza): risk of liver injury; new recommendations to minimise risk

Specialisms: *Obstetrics, gynaecology and fertility, General practice, Dispensing GP practices*

Summary

Fezolinetant treatment is associated with a risk of drug induced liver disease. New recommendations have been introduced to minimise this risk. Liver function should be monitored before and during treatment in all patients taking fezolinetant. Fezolinetant should be avoided in patients with known liver disease or at a higher risk of liver disease.

Advice for Healthcare Professionals:

- cases of serious liver injury with elevated transaminases, bilirubin and signs and symptoms of hepatic dysfunction have been reported during treatment with fezolinetant. These were generally reversible on discontinuation of therapy
- avoid fezolinetant in patients with known liver disease or patients at higher risk for liver disease
- treatment with fezolinetant must not be initiated if serum alanine aminotransferase (ALT) or serum aspartate aminotransferase (AST) levels are ≥2x the upper limit of normal or if total bilirubin levels are ≥2x the upper limit of normal
- treatment with fezolinetant must be discontinued if:
    - transaminase elevations are ≥3x the upper limit of normal with:
        total bilirubin >2x the upper limit of normal OR if patients develop symptoms of liver injury
    - transaminase elevations >5x the upper limit of normal
- perform liver function tests, including alanine aminotransferase (ALT), aspartate aminotransferase (AST), serum alkaline phosphatase (ALP) and serum bilirubin (total and direct), prior to treatment initiation, monthly during the first 3 months of treatment and periodically thereafter based on clinical judgment
- liver function tests must also be performed when signs or symptoms suggestive of liver injury occur
- monitoring should be maintained until liver function tests have normalised
- patients should be advised to seek immediate medical attention if they develop any sign or symptoms of liver injury, including fatigue, pruritus, jaundice, dark urine, pale faeces, nausea, vomiting, decreased appetite and/or abdominal pain

Advice for Healthcare Professionals *continued*:

- a Direct Healthcare Professional Communication (DHPC) has been disseminated alongside this Drug Safety Update
- report suspected adverse drug reactions associated with fezolinetant via the Yellow Card scheme

Advice for Healthcare Professionals to Provide to Patients:

- fezolinetant is used for the treatment of moderate to severe vasomotor symptoms, including hot flushes and night sweats, associated with the menopause
- there have been cases of liver problems in people taking fezolinetant, which were generally reversible following discontinuation of treatment
- all patients will now have their liver function tested before and during treatment
- you will have a blood test to check your liver function before you start taking fezolinetant. This will be repeated monthly during the first 3 months of treatment and then afterwards depending on when your doctor deems appropriate
- seek medical attention immediately if you develop symptoms suggesting a problem with your liver. These include tiredness, itching, yellowing of the skin and eyes, dark urine, light-coloured stools, feeling or being sick, loss of appetite or stomach pain
- always read the leaflet that is provided alongside your medicine, which contains information about taking fezolinetant and a full list of known possible side effects
- report suspected adverse drug reactions to the Yellow Card scheme

Background

Fezolinetant and liver injury

Fezolinetant is indicated for the treatment of moderate to severe vasomotor symptoms associated with the menopause. It is a nonhormonal selective neurokinin (NK) 3 receptor antagonist that blocks NKB binding on the KNDy neuron to modulate neuronal activity in the thermoregulatory centre.

The current product information contains information relating to ALT and AST elevations which were seen in clinical trials, and monitoring for some patients has been advised since its authorisation.

A recent European review of safety data identified 3 cases where ALT and/or AST elevations were accompanied by an increase in bilirubin and 12 cases where rises in transaminases were accompanied by additional signs and symptoms of liver injury such as pale stool, itching of palms and soles, abdominal pain and dark urine.

It is not possible to estimate the frequency of reports of liver injury or bilirubin elevations. Elevated ALT and AST are listed as common side effects meaning this occurs in more than

1 in 100 people but less than 1 in 10. The mechanism underlying liver injury following treatment is unknown.

In the UK, from December 2023 to January 2025 the Yellow Card scheme has received one spontaneous report of abnormal liver test results associated with fezolinetant; no spontaneous reports have been received for liver disorders.

Fezolinetant is currently only available through a private prescription.

As for all medicines, the MHRA will keep reports of suspected adverse drug reactions under close review.

New advice to minimise risk of liver injury

Following the findings of the European review, existing warnings on hepatotoxicity in the product information for fezolinetant have been strengthened. A recommendation has been added to perform liver function tests prior to treatment initiation, monthly for the first 3 months and periodically thereafter based on clinical judgment. Fezolinetant should be avoided in patients with a known liver condition or patients at higher risk for liver disease. A Direct Healthcare Professional Communication (DHPC) has been published.

Advice in cases of liver enzyme abnormalities

Elevated liver function tests (LFTs) and symptoms suggestive of liver injury were generally reversible on discontinuation of therapy.

Treatment should not be started if ALT and/or AST is ≥2x equal to or greater than two times the amount of upper limit of normal (ULN) or if total bilirubin is elevated for example bilirubin that is equal to or greater than two times the total amount of ULN (≥2x ULN).

Treatment should be stopped if liver injury is suspected, or if there is evidence of deranged liver function tests and monitoring of liver enzymes should be maintained until they have normalised.

Reporting advice

Healthcare professionals, patients, and caregivers are asked to submit reports using the Yellow Card scheme electronically using:

- the Yellow Card website.
- the Yellow Card app; download from the Apple App Store or Google Play Store
- some clinical IT systems for healthcare professionals (EMIS, SystmOne, Vision, MiDatabank, and Ulysses)

When reporting suspected adverse drug reactions, please provide as much information as possible, including information about medical history, any concomitant medication, onset timing, and treatment dates.

Additional information

You can sign up to receive email notifications for Drug Safety Updates.

You can sign up to receive our monthly round-up of safety communications.

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