

The United Kingdom: Fezolinetant (Veoza): risk of liver injury; new recommendations to minimise risk

Medicines and Healthcare products Regulatory Agency (MHRA) announces that 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.

Fezolinetant is indicated for the treatment of moderate to severe vasomotor symptoms associated with the menopause. The current product information contains information relating to alanine aminotransferase (ALT) and aspartate aminotransferase (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.

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.

Elevated liver function tests and symptoms suggestive of liver injury were generally reversible on discontinuation of therapy. Treatment should not be started if ALT and/or AST is $\geq 2x$ 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 ($\geq 2x$ 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.

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 ALT or serum AST levels are $\geq 2x$ the upper limit of normal or if total bilirubin levels are $\geq 2x$ the upper limit of normal.
- Treatment with fezolinetant must be discontinued if:
 - transaminase elevations are $\geq 3x$ 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 ALT, 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.
- A Direct Healthcare Professional Communication has been disseminated alongside this Drug Safety Update.

Please refer to the following website in MHRA for details:

<http://www.gov.uk/drug-safety-update/fezolinetantv-veoza-risk-of-liver-injury-new-recommendations-to-minimise-risk>

In Hong Kong, the above product is not a registered pharmaceutical product. Related news was previously issued by the United States Food and Drug Administration and European Medicines Agency, and was posted on the Drug Office website on 13 Sep 2024 and 30 Nov 2024.

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