DRUG UPDATE

Fezolinetant: Newer Non-hormonal Treatment of Vasomotor Symptoms

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Fezolinetant is a neurokinin 3 (NK3) receptor antagonist. It is the first non-hormonal drug for hot flashes at menopause, and was approved by the United States Food and Drug Administration in May 2023 and Medicines and Healthcare Products Regulatory Agency (MHRA) of UK for moderate to severe vasomotor symptoms associated with menopause.

Mechanism of Action

Fezolinetant blocks neurokinin B (NKB) binding on the kisspeptin/neurokinin B/dynorphin (KNDy) neuron to modulate neuronal activity in the thermoregulatory center. Fezolinetant has a high affinity for the NK3 receptor compared with NK1 or NK2 receptors. The thermoregulatory center (median preoptic nucleus) in the hypothalamus has the nerve supply from KNDy neurons. These are inhibited by estrogen through the nuclear estrogen receptor (ERα) and stimulated by neurokinin B via the NK3 receptor. Therefore, normal cooling will happen in the periphery as there is a balance. This occurs before menopause. At menopause, low estrogen results in the unopposed activity of neurokinin B and hypertrophy of KNDy neurons, which signals to the thermoregulatory center.

The recommended dose is a single 45 mg tablet orally once daily and can be given irrespective of the food. A missed dose should be taken as soon as possible, up to 12 hours before the next dose. Follow the usual schedule the next day. Baseline liver function tests should be done and to be followed up at 3, 6, and 9 months after treatment and when symptoms of liver injury are suspected.

The following adverse drug reactions were reported when the drug effect was studied for 52 weeks:

- Abdominal pain
- Diarrhea
- Insomnia
- Back pain
- Hot flush
- Hepatic transaminase elevation

Contraindications

- Known cirrhosis
- Severe renal impairment or end-stage renal disease
- Concomitant use with CYP1A2 inhibitors (examples include ciprofloxacin, fluvoxamine, etc.)

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Drug Interactions

Fezolinetant is a substrate of CYP1A2. The use of fezolinetant with drugs that are weak, moderate, or strong CYP1A2 inhibitors can increase the plasma Cmax (maximum concentration) and area under the curve (AUC) of fezolinetant. Hence, its use is contraindicated in persons taking CYP1A2 inhibitors.

Cautious use is recommended in renal impairment.

Contraindicated in patients with severe renal impairment (eGFR 15 to <30 mL/min/1.73 m^2) or end-stage renal disease (eGFR <15 mL/min/1.73 m^2). No dose adjustment is required for individuals with mild or moderate renal impairment. Hepatic transaminase elevation: alanine aminotransferase and/or aspartate transaminase levels were elevated and greater than three times the upper limit of normal. Women with raised hepatic transaminases were generally asymptomatic. These high levels came back to pretreatment levels without any sequelae despite continuation of dose or dose interruption or discontinuation. No elevations in serum total bilirubin were found.