

Medication Safety Update

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Clinical trials are a valuable pathway to identifying medication safety issues; however, selection of patients with specific characteristics and short trial durations are limitations in determining the risks in broader populations and long-term use. Post-marketing reports of adverse reactions are integral to safe prescribing practices. The Food and Drug Administration (FDA) releases important drug updates to alert providers of safety findings after drugs have been approved. These findings can include newly identified safety issues or removal of previously assigned warnings. Medication safety concerns also include the rise of online pharmacies selling prescription drugs. This newsletter will discuss new safety warnings, changes to drug labeling and risks to obtaining medications online.

Newly Identified Warnings

Glatiramer (COPAXONE[®], GLATOPA[®])

Glatiramer is a drug used for the treatment of relapsed multiple sclerosis (MS).¹ In January 2025, the FDA issued a safety alert for glatiramer on the risk of anaphylaxis, leading to hospitalization and death.² The risk is rare but can occur at any time during glatiramer therapy, from the first injection to months or years after starting therapy. The reported median time to onset of anaphylaxis was 5 months. Symptoms of allergic reaction usually occur within one hour of injection.² The FDA is adding this risk as part of a new *Boxed Warning* to glatiramer prescribing information.¹

Glatiramer is injected once daily or 3 times weekly.¹ Allergic symptoms can present similarly to common adverse reactions associated with glatiramer post-injection.¹ The immediate post-injection reactions occurred in 16% of glatiramer 20 mg/mL treated patients compared to 4% of placebo treated patients in clinical studies.¹ Post-injection reactions can present within seconds to 1 hour after administration and include: flushing, chest pain, palpitations, tachycardia, anxiety, dyspnea, constriction of the throat and urticaria.¹ Most symptoms are transient and don't require any intervention. Since these symptoms overlap with anaphylaxis symptoms it is important to not delay treatment if anaphylaxis is suspected.

Fezolinetant (VEOZAH[®])

Fezolinetant is a neurokinin 3 (NK3) receptor antagonist used for moderate to severe vasomotor symptoms due to menopause.³ In September 2024, the FDA issued a safety warning on the risk of serious liver injury.⁴ The new warning is accompanied with the recommendation to increase liver

function testing (LFTs) to monthly tests for the first 2 months following initiation and then at months 3, 6 and 9 of treatment.⁴

The new recommendation is in response to one case report of a woman with elevated LFTs (e.g., alanine aminotransferase [ALT], aspartate aminotransferase [AST], alkaline phosphatase [ALP] and total bilirubin) diagnosed with acute mixed hepatocellular cholestatic drug-induced liver injury. The event occurred within 40 days of initiation of fezolinetant. Hepatic enzymes returned to normal levels after medication discontinuation.⁴

Fezolinetant should be discontinued if there are symptoms of hepatic dysfunction to avoid worsening hepatic injury and increase the likelihood of reversal and restoration of normal hepatic function. Symptoms of liver injury included feeling fatigued, nausea, vomiting, unusual itching, light-colored stools, jaundice and swelling or pain in the abdomen.⁴

Fezolinetant should not be started in patients with LFTs that exceed two times the upper limit of normal (ULN).³

Additionally, fezolinetant should be stopped if LFTs exceed five times the ULN or if LFTs exceed three times the upper limit of normal and total bilirubin is more than two times the ULN.³

GLP-1 RAs

Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) are used most often for the treatment of type 2 diabetes (T2D) and in adults with overweight or obesity. The FDA is performing an ongoing evaluation of the risk of suicidal thoughts or actions in patients taking GLP-1 RAs.⁵ An initial review has not demonstrated evidence of an increased risk. The FDA is continuing to monitor reports to the FDA Adverse Event Reporting System (FAERS), as the small number of reports of suicidal thoughts in patients treated with GLP-1 Ras, and in those in control groups, could have failed to identify a potential small risk to patients.⁵ Providers should report any suicidal thoughts, worsening of depression or other changes in mood identified in patients taking GLP-1 RAs.⁵

Levetiracetam (KEPPRA[®]) and Clobazam (ONFI[®])

Levetiracetam and clobazam are antiseizure medications. Levetiracetam can be used as monotherapy or in combination with other medications for partial seizures, myoclonic seizures or tonic-clonic seizures.⁶ Clobazam is a benzodiazepine approved for seizures due to Lennox-Gastaut syndrome.⁷ In November 2023, the FDA released a safety warning on the risk of Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) with both levetiracetam and clobazam.⁸ Prescribing information for levetiracetam has added the risk of DRESS to

the *Warnings and Precautions* section. Clobazam will have prescribing information updated to include a new warning specifically related to DRESS.⁸

Severe inflammation is the underlying pathology associated with DRESS. Symptoms of DRESS may start with a rash but can progress to organ injury in the liver, kidneys, lungs, heart, or pancreas, leading to hospitalization and death.⁸ Patients should be counseled to seek emergency care if they have an unexplained rash, fever, or swollen lymph nodes. Rash may or may not be visible with the onset of DRESS.⁸ The occurrence of DRESS can occur during any time while taking these medications, but it is most reported within 2 to 8 weeks of starting therapy. Patients should also be made aware of the risk of Stevens-Johnson Syndrome (SJS) and toxic epidermal necrolysis (TEN) which have also been reported with both levetiracetam and clobazam.⁸

The new warnings of DRESS associated with levetiracetam and clobazam were a result of a medical literature search and reports to the FAERS database.⁸ The incidence of DRESS was identified in 32 adults and children taking levetiracetam and 10 adults and children taking clobazam. Two patients taking levetiracetam died and all patients taking either levetiracetam or clobazam required hospitalization.⁸ The most common symptoms were rash and fever. Other benzodiazepines do not have the same association with DRESS and other serious skin conditions.

Warning Removal

Clozapine (CLOZARIL®)

Clozapine is an effective antipsychotic with limited use due to risks of severe neutropenia. Until recently, prescribers, pharmacies and patients were required to participate in the Risk Evaluation and Mitigation Strategies (REMS) program for clozapine.⁹ The REMS program required absolute neutrophil count (ANC) blood tests before dispensing clozapine. The REMS requirement was removed by the FDA in February 2025 to increase access to clozapine.¹⁰

Clozapine still carries a boxed warning for the risk of agranulocytosis, orthostatic hypotension, bradycardia, syncope, seizures, myocarditis and cardiomyopathy, and increased mortality in elderly patients with dementia-related psychosis.⁹ The FDA recommends that ANC still be monitored as described in the labeling. The ANC should be monitored weekly for 6 months upon clozapine initiation, every 2 weeks for 6-12 months and every 4 weeks for treatment durations of 12 months and beyond.⁹ Additional monitoring recommendations are available in the prescribing information for patients with abnormal hematological values and when discontinuing clozapine therapy.⁹ Information on the use of clozapine for schizophrenia is available from the Oregon Mental Health Clinical Advisory Group: [Treatment of Schizophrenia with Antipsychotic Medications](#).

Online Medication Safety

Many patients are obtaining medications online due to supply issues, lower cost alternatives and discreetness of ordering. With the increase in this practice, safety issues have been identified. The Center for Disease Control (CDC) has announced a public health risk related to counterfeit medications from online pharmacies.¹¹ The United States Department of Justice (DOJ) has indicted individuals for advertising, selling, manufacturing, and shipping unregulated counterfeit prescription medications. Often these drugs contain fentanyl and methamphetamine.¹¹

Online pharmacies offer prescription drugs at reduced prices and without a prescription. The National Association of Boards of Pharmacy (NABP) report that almost 95% of prescription-only online pharmacies are operating illegally and 96% of these pharmacies did not require a prescription to obtain a prescription medication.¹²

Characteristics of an Illegal Online Pharmacy¹¹

- No prescription required
- Medication prices are much lower than other pharmacies
- Not a licensed pharmacy in the U.S. or state-licensed online pharmacy
 - Authorized online pharmacies can be found at: [Locate a State-Licensed Online Pharmacy](#)

Many patients are obtaining medications for weight loss from online pharmacies. Most commonly patients seek GLP-1 RAs, such as semaglutide, for this purpose; however, these pharmacies also offer oral medications. Online sites, such as *ForHers*, offer medication kits containing topiramate, bupropion XL, metformin, vitamin B12 and naltrexone with an online provider consult.¹³ Providers should inquire if patients are obtaining medications through online sites and educate patients on appropriate use and screen for drug interactions and/or duplicate therapy.

Reporting Adverse Events

Reporting safety issues to the FDA MedWatch program is an important component of identifying medication safety concerns after a drug has been approved. Providers can report adverse events at [MedWatch](#).

Conclusion

Medication safety updates are a component of staying current with prescribing recommendations and trends in consumer patterns. Recognizing early signs of serious adverse events is critical to seeking appropriate medical care and should be discussed with patients. Patients should be educated on the importance of getting medication from a licensed online pharmacy to avoid unnecessary risks.

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