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Levetiracetam (Keppra®, Keppra XR®, Elepsia™ XR, Spritam®) and clobazam (Onfi®, Sympazan™) – FDA drug safety communication

- On November 28, 2023, the FDA warned that the antiseizure medicines levetiracetam (Keppra, Keppra XR, Elepsia XR, Spritam, and generics) and clobazam (Onfi, Sympazan, and generics), can cause a rare but serious reaction that can be life-threatening if not diagnosed and treated quickly.
    - This reaction is called Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS). It may start as a rash but can quickly progress, resulting in injury to internal organs, the need for hospitalization, and even death. As a result, the FDA is requiring warnings about this risk to be added to the prescribing information and patient Medication Guides for these medicines.

- The warnings for both levetiracetam and clobazam medicines will include information that early symptoms of DRESS such as fever or swollen lymph nodes can be present even when a rash cannot be seen. This is different from other serious skin-related reactions that can happen with these medicines and where a rash is present early on, including Stevens-Johnson Syndrome (SJS) and toxic epidermal necrolysis (TEN).

- Levetiracetam is an antiseizure medicine approved for use alone or with other medicines to control certain types of seizures.

- Clobazam is a type of medicine called a benzodiazepine that is FDA-approved for use with other medicines to control seizures associated with a specific severe form of epilepsy called Lennox-Gastaut Syndrome.

- For levetiracetam, a search of the FDA Adverse Event Reporting System (FAERS) and the medical literature through March 2023 identified 32 serious cases of DRESS worldwide. Three cases occurred in the U.S. and 29 abroad. In all 32 cases, the patients were hospitalized and received medical treatment; in two cases the patients died.
    - The median time to onset was 24 days (range 7 to 170 days).
    - The reported signs and symptoms included skin rash (n=22), fever (n=20), eosinophilia (n=17), lymph node swelling (n=9), and atypical lymphocytes (n=4).
    - Twenty-two cases reported injury to one or more organs, including the liver (n=20), lungs (n=4), kidneys (n=3), and gallbladder (n=1).
    - Twenty-five of the 29 cases for which information on treatment discontinuation was available reported that DRESS symptoms resolved when levetiracetam was discontinued.

- For clobazam, a search of FAERS and the medical literature through July 2023 identified 10 serious cases of DRESS worldwide, one in the U.S. and nine abroad. In all 10, the patients were hospitalized and received medical treatment. No deaths were reported.
    - The median time to onset was 21.5 days (range 7 to 103 days).
    - The reported signs and symptoms included skin rash (n=10), fever (n=8), eosinophilia (n=7), facial swelling (n=7), leukocytosis (n=4), lymph node swelling (n=4), and leukopenia/thrombocytopenia (n=1).
    - Nine cases reported injury to one or more organs, including the liver (n=7), kidneys (n=3), and gastrointestinal tract (n=1).
    - DRESS symptoms resolved in all 10 when clobazam was discontinued.

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  - DRESS and other serious skin reactions reported with clobazam have not generally been associated with other benzodiazepines.

- Patients and their caregivers should not stop taking or giving levetiracetam or clobazam without talking with their health care professional.

  - Stopping these medicines suddenly can lead to uncontrolled seizures.
  - It is important to seek immediate medical attention for DRESS.
  - Patients who develop any unusual symptoms or reactions, including a rash, at any time while taking levetiracetam or clobazam should go to an emergency room immediately.
  - Symptoms of DRESS generally start 2 weeks to 8 weeks after starting on the medicine, but these symptoms may occur earlier or later.

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