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(來函請敍明此檔案號碼) DH DO DIMC/7-30/1
(IN REPLY PLEASE QUOTE THIS FILE REF.)

29 Nov 2023

Dear Healthcare Professionals,

FDA warns of rare but serious drug reaction to the antiseizure medicines levetiracetam (Keppra, Keppra XR, Elepsia XR, Spritam) and clobazam (Onfi, Sympazan)

Your attention is drawn to the United States Food and Drug Administration's (FDA) announcement that the antiseizure medicines levetiracetam (Keppra, Keppra XR, Elepsia XR, Spritam) and clobazam (Onfi, Sympazan) 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.

This hypersensitivity reaction to these medicines is serious but rare. DRESS can include fever, rash, swollen lymph nodes, or injury to organs including the liver, kidneys, lungs, heart, or pancreas.

FDA is requiring manufacturers of these medicines to add new warnings about DRESS to the prescribing information and the medication guide for patients and caregivers. For levetiracetam, this involves adding a new warning in the Warnings and Precautions section of the prescribing information, which describes the most serious and significant potential safety issues. Currently the symptoms associated with this condition are described less prominently. For clobazam, FDA is requiring a new warning specifically about DRESS to be added to the prescribing information. Symptoms related to this risk are already described more generally in other sections of the clobazam prescribing information.

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). FDA is also requiring information on this risk to be added to the medication guides to help inform patients and caregivers about this risk.

FDA's cumulative review found serious cases of DRESS in children and adults worldwide (32 for levetiracetam and 10 for clobazam). Most patients in these cases required hospitalization and received medical treatments, and two patients treated with levetiracetam died. These numbers include only reports submitted to FDA and found in the medical literature, so there are likely additional cases about which FDA is unaware. FDA determined there was reasonable evidence that levetiracetam and clobazam were the cause of DRESS in these cases based on the timing of the onset of these events after receiving the medicines and the order in which they occurred. The majority of cases for which information about discontinuation was available reported that DRESS symptoms improved when the medicines were discontinued.

Health care professionals should be aware that prompt recognition and early treatment is important for improving DRESS outcomes and decreasing mortality. Diagnosis is often difficult because early signs and symptoms such as fever and swollen lymph nodes may be present without evidence of a rash. DRESS can develop 2 weeks to 8 weeks after starting the medicines, and symptoms and intensity can vary widely. DRESS can also be confused with other serious skin reactions such as SJS and TEN. Advise patients of the signs and symptoms of DRESS and to stop taking their medicine and seek immediate medical attention if DRESS is suspected during treatment with levetiracetam or clobazam.

Please refer to the following website in FDA for details:
https://www.fda.gov/drugs/drug-safety-and-availability/fda-warns-rare-serious-drug-reaction-antiseizure-medicines-levetiracetam-keppra-keppra-xr-elepsia-xr

In Hong Kong, there are registered pharmaceutical products containing levetiracetam (38 products) and clobazam (3 products). All products are prescription-only medicines. So far, the Department of Health (DH) has received adverse drug reaction related to levetiracetam (7 cases) and clobazam (one case), but these cases were not related to DRESS.

Related news on the risk of DRESS associated with the use of clobazam was previously issued by Health Canada, and was posted on the Drug Office website on 10 Dec 2020. Letters to inform local healthcare professionals were issued by the DH on the same day. In Dec 2021, the Registration Committee of the Pharmacy and Poisons Board discussed the matter, and decided to keep vigilant on any update from other health authorities.

In light of the above FDA's announcement, the matter will be discussed by the Registration Committee of the Pharmacy and Poisons Board.

Please note that this letter serves as a means for the DH to communicate important new safety information about registered pharmaceutical products with healthcare professionals in Hong Kong and is not intended to serve as guidelines or to replace professional clinical judgement. Healthcare professionals are advised to balance the risk of possible adverse effects against the benefit of treatment.

Please report any adverse events caused by drugs to the Adverse Drug Reaction Unit of the DH (tel. no.: 2319 2920, fax: 2319 6319 or email: adr@dh.gov.hk). For details, please refer to the website at Drug Office under "ADR Reporting": http://www.drugoffice.gov.hk/adr.html. You may wish to visit the Drug Office's website for subscription and browsing of "Drug News" which is a monthly digest of drug safety news and information issued by Drug Office.

Yours faithfully,

(Terence MAN)
for Assistant Director (Drug)