SAFETY ALERT

DRAP SAFTEY ALERT NO. 40

Safety Alert of Risk of Seizures with Cephalosporins.

Date: 20th of October, 2023.

Target Audience:

- Manufacturers and importers of Cephalosporins antibiotics;
- Healthcare professionals; and
- Patients, consumers or caregivers.

Background:

Health Canada in January, 2023 announced that the product safety information for cephalosporins will be updated to include the risk of seizures in all the cephalosporins. As the risk of seizures was already included for some cephalosporins, this update was applied to cephalosporins that did not include the risk. The review was triggered by a US Food and Drug Administration update to the product safety information for cefazolin to include the risk of seizures. Accordingly, Health Canada reviewed the available information from searches of the Canada Vigilance database, international databases, as well as medical and scientific literature. Health Canada reviewed 84 cases (7 domestic and 77 international) of seizures in patients taking cephalosporins. Of the 84 cases, 13 cases (all international) were found to be probably linked to the use of cephalosporins, and 62 cases (4 domestic and 58 international) were found to be possibly linked. Three cases (all international) were unlikely to be linked to the use of cephalosporins. Six cases (3 domestic and 3 international) could not be assessed. The review concluded that there may be a link between the use of cephalosporins and the risk of seizures and therefore the agency informed that it would work with manufacturers to update the Canadian Product Monographs for the cephalosporins that did not already include the risk.

The New Zealand Medicines and Medical Devices Safety Authority (Medsafe) in its publication dated 2nd March, 2023 informed that the risk of neurotoxicity with cephalosporins was discussed at the December 2022 Medicines Adverse Reaction Committee (MARC) meeting wherein the committee recommended that all cephalosporin data sheets should include consistent messaging on the risk of neurotoxicity. Cephalosporin-induced neurotoxicity may present in a range of

conditions which are mainly characterised by encephalopathy, myoclonus and/or seizures. Seizures associated with cephalosporins may present as either convulsive or non-convulsive. Symptoms of neurotoxicity have been reported to develop within several days after starting treatment and to resolve following discontinuation. In patients with renal impairment, accumulation can occur, especially when doses are not adjusted appropriately, potentially leading to toxic effects. Additional risk factors for cephalosporin-induced neurotoxicity include older age groups, underlying central nervous system (CNS) disorders and high doses of cephalosporins administered by intravenous injection.

Action in Pakistan:

The case was discussed in the 3rd meeting of PRAEC, held on the 8th of September, 2023, which decided as per Rule 10(1)(h)(iv) of the Pharmacovigilance Rules, 2022 that the registration holders of all cephalosporins should include information on the risk of seizures/ neurotoxicity in the warning and precaution section and also list in adverse drug reaction section in the prescribing information/label of all cephalosporins.

Therapeutic Goods Affected.

Name: **Cephalosporins** are a group of prescription antibiotic medicines (cephalexin, cefazolin, cefadroxil, cefuroxime, cefprozil, cefotaxime, ceftazidime, ceftriaxone, cefixime and cefepime) and are indicated for the treatment of a wide range of bacterial infections including urinary and respiratory tract infections.

Advice for patients.

Patients are advised to take their antibiotic for the recommended duration and indication and promptly notify their healthcare professional about any signs of seizures/ neurotoxicity they experience.

Advice for healthcare professionals.

Seizures may occur with the administration of Cefazolin for Injection, particularly in patients with renal impairment when the dosage is not reduced appropriately. Additional risk factors for cephalosporin-induced neurotoxicity include older age groups, underlying central nervous system (CNS) disorders and high doses of cephalosporins administered by intravenous injection. Discontinue the cephalosporin antibiotic if seizures occur or make the appropriate dosage

adjustments in patients with renal impairment. Anticonvulsant therapy should be continued in patients with known Seizure disorders.

Guidelines for reporting Adverse Drug Reactions (ADRs):

Both healthcare professionals and patients are requested to report any suspected adverse drug reaction (ADRs) with cephalosporins antibiotics to the National Pharmacovigilance Centre (NPC), Drug Regulatory Authority of Pakistan (DRAP) through the Med Vigilance E-Reporting System available on the DRAP website. Similarly, ADRs can also be reported through Med Safety App which is available for download from the App Store (for iOS devices) and Google Play (for Android devices).

References:

- Minutes of 3rd meeting of Pharmacovigilance Risk Assessment Expert Committee.
- Health Canada: Summary Safety Review - Cephalosporins - Assessing the Potential Risk of Seizures.
- Medsafe-New Zealand: Risk Of Neurotoxicity With Cephalosporins.