S

SAFETY ALERT

DRAP SAFTEY ALERT NO. 48

Safety Alert of Risk of Haemophagocytic Lymphohistiocytosis (HLH) with Sulfamethoxazole and Trimethoprim combination.

Date: 27th of April, 2024.

Target Audience.

- Manufacturers and importers of Sulfamethoxazole and Trimethoprim combination;
- Healthcare Professionals; and
- Patients, Consumers or Caregivers.

Background.

Health Canada in May 2023 announced that the product safety information for combination sulfamethoxazole and trimethoprim-containing products will be updated to include the risk of haemophagocytic lymphohistiocytosis (HLH). Triggered by a labelling update for these products by the EMA, Health Canada reviewed the available information from the Canadian and international databases, and the scientific literature. Of the ten cases assessed, one case was found to be probably linked to the use of the medicine, eight were found to be possibly linked (including one fatal case) and one (another fatal case) was unlikely to be linked. The review found a possible link between the use of the medicine and the risk of HLH. HLH is a life-threatening syndrome of pathologic immune activation characterised by clinical signs and symptoms of extreme systemic inflammation (e.g. fever, hepatosplenomegaly, hypertriglyceridaemia, hypofibrinogenaemia, high serum ferritin, cytopenias and haemophagocytosis) and is associated with high mortality rates if not recognised early and treated. Healthcare professionals were advised to immediately evaluate patients who develop early manifestations of pathologic immune activation. If HLH is diagnosed, discontinue sulfamethoxazole-trimethoprim treatment.

Previously, the Pharmacovigilance Risk Assessment Committee (PRAC) of the European Medicine Agency in its meeting from 03-06 May 2021 considered the available evidence in EudraVigilance, the literature, and the data submitted by Roche/ Eumedica, Aspen Pharma and Teva regarding the risk of Haemophagocytic lymphohistiocytosis (HLH) with sulfamethoxazole/trimethoprim in combination and agreed that the available information is considered sufficient to support a warning statement in the product information of the drug combination.

Action in Pakistan.

The case was discussed in the 4th meeting of the Pharmacovigilance Risk Assessment Expert Committee (PRAEC) of the DRAP held on 26th of February, 2024 which decided the case as per Rule 10 (1) (h) (iv) of Pharmacovigilance Rules, 2022 to update the warning and precaution section of the prescribing information/label of the drug combination of sulfamethoxazole and trimethoprim by including information about the risk of haemophagocytic lymphohistiocytosis (HLH).

Therapeutic Goods.

Name: Sulfamethoxazole plus Trimethoprim is a prescription antibiotic medicine indicated for the treatment of various bacterial infections, such as urinary tract infections, respiratory tract infections, and gastrointestinal infections.

Advice for Healthcare Professionals.

Healthcare professionals are informed that cases of HLH have been reported very rarely in patients treated with co-trimoxazole (Sulfamethoxazole+Trimethoprim). HLH is a life-threatening syndrome of pathologic immune activation characterised by clinical signs and symptoms of excessive systemic inflammation (e.g. fever, hepatosplenomegaly, hypertriglyceridaemia, hypofibrinogenaemia, high serum ferritin, cytopenias and haemophagocytosis). Patients who develop early manifestations of pathologic immune activation should be evaluated immediately. If a diagnosis of HLH is established, cotrimoxazole treatment should be discontinued.

Advice for Patients.

Patients are informed not to stop the medication without the advice of their healthcare professional and to immediately consult their healthcare professional if they experience any symptoms of HLH during treatment with sulfamethoxazole+trimethoprim.

Guidelines for reporting Adverse Drug Reactions (ADRs).

Both healthcare professionals and patients are requested to report any suspected adverse drug reaction (ADRs) with Sulfamethoxazole plus Trimethoprim drug combination 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 the 4th meeting of the Pharmacovigilance Risk Assessment Expert Committee.
- Summary Safety Review - Combination Sulfamethoxazole and Trimethoprim - Assessing the Potential Risk of Hemophagocytic Lymphohistiocytosis. Health Canada.
- EMA-PRAC recommendations on signals adopted on the 3-6th May 2021 meeting.