SAFETY ALERT

DRAP SAFTEY ALERT NO. 45

Safety Alert of Risk of Neurodevelopmental Disorders in Children during Pregnancy with Topiramate.

Date: 22nd of April, 2024.

Target Audience.

- Manufacturers and importers of Topiramate;
- Healthcare Professionals; and
- Patients, Consumers or Caregivers.

Background.

The Medsafe of Newzealand in April, 2023 has announced that the product information for topiramate (Topamax®) is updated to include the risk of neurodevelopmental disorders and birth defects in children whose mothers were taking topiramate during pregnancy. The risk of neurodevelopmental disorders was noted in an observational study based on data from five Nordic (Denmark, Finland, Iceland, Norway, and Sweden) pregnancy registries. The registries captured information from over 24,000 children exposed to at least one antiepileptic medicine before birth. Of these children, 471 were exposed to topiramate alone. The authors reported a 2.77-fold increase in the risk of autism spectrum disorder and a 3.47-fold increase in the risk of intellectual disability in children with an epileptic mother taking topiramate during pregnancy compared to those who are not taking any antiepileptic treatment during pregnancy.

The TGA, Australia in its product information safety update of June, 2023 has also announced that the product information for topiramate (Topamax®) is updated to include the risk of foetal neurodevelopment disorder, updated warning about women of childbearing potential, and contraindications in pregnancy and women of childbearing potential for migraine prophylaxis.

The European Medicine Agency (EMA) in July, 2023 started a review to assess new data on a potential risk of neurodevelopmental disorders in children who have been exposed to topiramate during pregnancy. At that time, a study based on data from a Nordic registry that investigated the risk of neurodevelopmental disorders associated with several anti-epileptic drugs, including topiramate was published. The study conclusions suggested a possible increase in the risk of autism spectrum disorders, intellectual disability and child neurodevelopmental disorders with the exposure to topiramate during pregnancy. The PRAC decided at that time that further

assessment was warranted to determine the scope and the best regulatory procedure to assess these potential risks.

Accordingly, the Pharmacovigilance Risk Assessment Committee (PRAC) (EMA's safety committee) in September, 2023 introduced further restrictions i.e. pregnancy prevention programme on the use of topiramate to be put in place. At present, topiramate must not be used to prevent migraine or manage body weight during pregnancy and patients who can become pregnant must use effective birth control when using topiramate. For patients using topiramate for the treatment of epilepsy, the PRAC is now recommending that the medicine should not be used during pregnancy unless there is no other suitable treatment available. The PRAC also recommends additional measures, in the form of a pregnancy prevention programme, to avoid exposure of children to topiramate in the womb. These measures will inform any woman or girl who is able to have children about the risks of taking topiramate during pregnancy and the need to avoid becoming pregnant while taking topiramate. The product information for topiramate-containing medicines will be updated to further highlight the risks and the measures to be taken. A visible warning will also be added to the outer packaging of the medicine. Patients and healthcare professionals will be provided with educational materials regarding the risks of using topiramate during pregnancy, and a patient card will be provided to the patient with each medicine package. The PRAC recommendations were sent to the Co-ordination Group for Mutual Recognition and Decentralized Procedures for Human (CMDH), which on 11 October 2023 endorsed new measures recommended by EMA's safety committee (PRAC). The CMDh has also agreed to additional measures, in the form of a pregnancy prevention programme, to avoid exposure of children to topiramate in the womb.

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, that registration holders should update the prescribing information of Topiramate to include the risk of foetal neurodevelopment disorder and warning about women of childbearing potential, and also include information about not using the Topiramate in pregnancy for the treatment of epilepsy unless there is no other suitable treatment available. Furthermore, registration holders were also directed as per Rule 10 (1) (h) (ii) of Pharmacovigilance Rules, 2022 to update contraindications in pregnancy and women of childbearing potential for migraine prophylaxis.

Therapeutic Good.

Name: **Topiramate** is a medicine used to treat epilepsy in adults and children aged two years and older. It is also indicated in adults for the prevention of migraines. At present, topiramate must not be used to prevent migraine or manage body weight during pregnancy and patients who can become pregnant must use effective birth control when using topiramate.

Advice for Healthcare Professionals.

Healthcare professionals are advised that topiramate should only be used to treat epilepsy in pregnancy if the potential benefit justifies/outweighs the potential risk to the mother and fetus. Pregnancy testing should be performed before starting treatment, and women of childbearing potential should use a highly effective contraceptive method during treatment. The use of topiramate for migraine prophylaxis is contraindicated in pregnancy. Inform women of childbearing potential about the risks of fetal harm if they become pregnant and refer epileptic women taking topiramate who become or plan to become pregnant for specialist advice.

Advice for Patients.

Patients are advised not to stop taking topiramate without first talking to their doctor. Topiramate can harm the way an unborn baby grows and develops during pregnancy. Anyone who is able to get pregnant should use effective contraception while taking topiramate. Therefore, those patients are advised to speak with their doctor if they are pregnant or planning to become pregnant whilst taking taking topiramate.

Guidelines for reporting Adverse Drug Reactions (ADRs).

Both healthcare professionals and patients are requested to report any suspected adverse drug reaction (ADRs) with medicine containing topiramate 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 4th meeting of Pharmacovigilance Risk Assessment Expert Committee, DRAP.
- Therapeutic Goods Administration of Australia Safety Updates June 2023.
- PRAC-EMA recommendation regarding new measures to avoid topiramate exposure in pregnancy.
- MedSafe Newzealand-Topiramate use in pregnancy: further restrictions for safety.

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