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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.)

4 Sep 2023

Dear Healthcare Professionals,

PRAC recommends new measures to avoid topiramate exposure in pregnancy

Your attention is drawn to the European Medicines Agency's (EMA) announcement that its safety committee, the Pharmacovigilance Risk Assessment Committee (PRAC), recommends new measures to avoid exposure of children to topiramate-containing medicines in the womb, because the medicine may increase the risk of neurodevelopmental problems after exposure during pregnancy. Topiramate is already known to cause serious birth defects when used during pregnancy.

Topiramate-containing medicines are used in the European Union for the treatment of epilepsy and prevention of migraine. In some European Union countries, the medicine is also used in combination with phentermine for weight reduction. 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 of the risks of taking topiramate during pregnancy and the need to avoid becoming pregnant while taking topiramate.

Healthcare professionals should ensure that all patients who can become pregnant are fully aware of the risks of taking topiramate during pregnancy. Alternative treatment options should be considered and the need for topiramate treatment should be reassessed at least annually. The product information for topiramate-containing medicines will be updated to further highlight the risks and the measures to be

taken. 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. A visible warning will also be added to the outer packaging of the medicine.

The recommendations follow the PRAC's review of available data, including three recent observational studies. Two of these studies, which used largely the same datasets, suggest that children born to mothers with epilepsy and who were exposed to topiramate in the womb may have a two- to three-fold higher risk of neurodevelopmental disorders, in particular autism spectrum disorders, intellectual disability or attention deficit hyperactivity disorder (ADHD), compared with children born to mothers with epilepsy not taking antiepileptic medication. The third study did not show an increased risk of these outcomes in children born to mothers exposed to topiramate in pregnancy, compared with children born to women with epilepsy not taking antiepileptic medication.

In its review, the PRAC confirmed the known increased risk of birth defects and reduced growth of the unborn child when mothers receive topiramate during pregnancy. Birth defects will occur in 4 to 9 out of every 100 children born to women who take topiramate during pregnancy, compared with 1 to 3 out of every 100 children born to women who do not take such treatment. Further, around 18 in every 100 children were smaller and weighed less than expected at birth when mothers had taken topiramate during pregnancy, compared with 5 in every 100 children born to mothers without epilepsy and not taking antiepileptic medication.

The companies that market topiramate must carry out a drug utilisation study and surveys of healthcare professionals and patients to assess the effectiveness of the new measures.

The PRAC recommendations will now be sent to the Co-ordination Group for Mutual Recognition and Decentralised Procedures – Human (CMDh), which will adopt a position.

Information for healthcare professionals:

- It is already well known that topiramate can cause major congenital malformations and foetal growth restriction when used during pregnancy. Recent data also suggest a possibly increased risk of neurodevelopmental disorders following topiramate use during pregnancy.
- In the prevention of migraine and as treatment for weight management, topiramate is contraindicated during pregnancy. Topiramate must be discontinued if the patient becomes pregnant or is planning for a baby. Patients of childbearing potential should use highly effective contraception during treatment and for at least 4 weeks after stopping topiramate treatment.
- In the treatment of epilepsy, topiramate is contraindicated during pregnancy unless there is no suitable treatment alternative. Topiramate is also contraindicated in women of childbearing potential with epilepsy not using highly effective contraception. The only exception is a woman

for whom there is no suitable alternative but who is planning a pregnancy and who has been fully informed about the risks of taking topiramate during pregnancy.

- Irrespective of indication, topiramate should be used in women of childbearing potential only when the following conditions of the pregnancy prevention programme are met: a pregnancy test before starting treatment; counselling about the risks of topiramate treatment and the need for highly effective contraception throughout treatment; a review of ongoing treatment at least annually by completion of a risk awareness form.
- To confirm that appropriate measures have been taken, patients and prescribers will go through this form at the beginning of treatment and at each annual review and if the patient is planning a pregnancy or has become pregnant. It should be ensured that the patient is fully informed and has understood the risks and measures to be taken.
- Topiramate treatment of patients of childbearing potential should be initiated and supervised by a physician experienced in the management of epilepsy or migraine. Treatment with topiramate/phentermine should be handled by a physician experienced in weight management. Alternative therapeutic options should be considered and the need for treatment should be reassessed together with the patient at least annually. Ongoing treatment should be re-evaluated to confirm that the measures outlined above have been taken.

Please refer to the following website in EMA for details:
https://www.ema.europa.eu/en/news/prac-recommends-new-measures-avoid-topiramate-exposure-pregnancy

In Hong Kong, there are 26 registered pharmaceutical products containing topiramate. All products are prescription-only medicines. So far, the Department of Health (DH) has received 5 cases of adverse drug reaction related to topiramate, but these cases were not related to neurodevelopmental disorders in children exposed to topiramate in utero.

Currently, the package insert and/or sales pack label of locally registered topiramate-containing products should include safety information on fetal harm and the increased risk of cleft lip and/or cleft palate (oral clefts) in infants exposed to topiramate in utero.

Related news on the risk of neurodevelopmental disorders in children exposed to topiramate in utero was previously issued by various overseas drug regulatory authorities, and was posted on the Drug Office website since 9 Jul 2022, with the latest update posted on 7 Mar 2023.

In light of the above EMA'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)