Drug News
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This is a monthly digest of local and overseas drug safety news released by the Drug Office of the Department of Health in July 2022 with relevant information update before publish. For the latest news and information, please refer to public announcements or the website of the Drug Office of the Department of Health (http://www.drugoffice.gov.hk).

Safety Update

European Union: Medicines containing nomegestrol or chlormadinone: PRAC recommends new measures to minimise risk of meningioma

On 8 July 2022, European Medicines Agency (EMA) announced that its Pharmacovigilance Risk Assessment Committee (PRAC) has recommended new measures to minimise the risk of meningioma with medicines containing nomegestrol or chlormadinone, which are used for gynaecological and menstrual disorders, hormone replacement therapy and, at lower doses, as hormonal contraceptives (birth control). Meningioma is a tumour of the membranes covering the brain and spinal cord. It is usually benign and is not considered to be a cancer, but due to their location in and around the brain and spinal cord, meningiomas can in rare cases cause serious problems.

The PRAC has recommended that medicines containing high-dose chlormadinone (5 – 10 mg) or high-dose nomegestrol (3.75 – 5 mg) should be used at the lowest effective dose and for the shortest duration possible, and only when other interventions are not appropriate. In addition, low- and high-dose nomegestrol or chlormadinone medicines must not be used by patients who have, or have had, meningioma.

As well as restricting the use of the high-dose medicines, the PRAC has recommended that patients should be monitored for symptoms of meningioma, which can include change in vision, hearing loss or ringing in the ears, loss of smell, headaches, memory loss, seizures and weakness in arms or legs. If a patient is diagnosed with meningioma, treatment with these medicines must be permanently stopped.

The product information for the high-dose medicines will also be updated to include meningioma as a rare side effect.

The recommendations follow a review of available data, including post-marketing safety data and results from two recent epidemiological studies. These data showed that the risk of meningioma increases with increasing dose and duration of treatment.

The PRAC recommendations will be sent to the Committee for Medicinal Products for Human Use (CHMP) for the adoption of EMA's final opinion.

In Hong Kong, there is no registered pharmaceutical product containing nomegestrol. There is 1 registered pharmaceutical product (HK-65918) containing chlormadinone in combination with ethinyloestradiol in tablet dose form. The product is a prescription-only medicine. As of the end of July 2022, the Department of Health (DH) had not received any cases of adverse drug reaction related to chlormadinone. Related news was previously issued by EMA, and was reported in Drug News Issue No. 144. In light of the above EMA's announcement, the DH issued letters to inform local healthcare professionals to draw their attention on 11 July 2022. As the above PRAC's recommendation will be sent to CHMP for further endorsement, the DH will remain vigilant on the development of the issue and any safety update of the drug issued by other overseas drug regulatory authorities.

Australia: First-generation oral sedating antihistamines - do not use in children

On 13 July 2022, Therapeutic Goods Administration (TGA) announced that with the arrival of winter and flu season in Australia,

consumers and health professionals are reminded that first-generation oral sedating antihistamines, including those available over-the-counter (OTC), should not be used for the treatment of cough, cold and flu symptoms in children under 6 years. First-generation oral sedating antihistamines should not be given to children under 2 years of age for any indication. These medicines can cause children serious harm, or even death, and there is little if any evidence that they are effective in treating cough, cold and flu symptoms.

Since 1 September 2020, all OTC products containing first-generation oral sedating antihistamines have been required to carry warnings that state 'Do not give to children under 2 years of age'. Oral preparations for coughs, cold or flu must also carry warnings stating: 'Do not give to children under 6 years of age' and 'should only be given to children aged 6 to 11 years on the advice of a doctor, pharmacist or nurse practitioner'.

The TGA's independent Advisory Committee on Medicines (ACM) has advised that there is minimal if any evidence supporting efficacy of first-generation oral sedating antihistamines for allergic rhinitis and cough and cold symptoms in children.

The committee reinforced the importance of health professionals providing thoughtful diagnosis, advice and treatment of allergy, cold and flu symptoms in children. They also reiterated that it is inappropriate to use antihistamines for sleep and behaviour disturbance, especially in children and adolescents.

To 24 May 2022, 226 cases involving use of first-generation oral sedating antihistamines in newborns, infants and children were reported to the TGA. The reports included a range of adverse events, including hypersensitivity reactions, vomiting, hallucination, tremor and abnormal movement. Of the 226 cases, 20 related to off-label use, misuse or overdose in children 4 years and under.

First-generation oral sedating antihistamines include products containing the following active ingredients:
- alimemazine (trimeprazine)
- brompheniramine
- chlorphenamine
- dexchlorpheniramine
- diphenydramine
- doxylamine
- pheniramine
- promethazine
- triprolidine

These products are indicated for multiple conditions, including the treatment of symptoms for cold, flu, cough and allergy.

In Hong Kong, there are registered oral pharmaceutical products containing brompheniramine (103 products), chlorphenamine (788 products), dexchlorpheniramine (106 products), diphenydramine (61 products), doxylamine (2 products), pheniramine (2 products), promethazine (237 products) and triprolidine (43 products). They are all non-prescription medicines, except doxylamine which is a prescription-only medicine. There is no registered pharmaceutical product containing alimemazine (trimeprazine).

As of the end of July 2022, the Department of Health (DH) had received one adverse drug reaction report related to brompheniramine for children under 2 years of age, which involved abnormal movement of the eyeball. In light of the above TGA's announcement, the DH issued letters to inform local healthcare professionals to draw their attention on 13 July 2022. The DH will remain vigilant on any safety update of the drugs issued by other overseas drug regulatory authorities for consideration of any action deemed necessary.

Canada: Summary Safety Review: Cholinesterase inhibitors (donepezil-, rivastigmine- and galantamine-containing products) - Assessing the potential risk of QT interval prolongation and torsade de pointes

On 19 July 2022, Health Canada announced that it reviewed the risk of QT interval prolongation and torsade de pointes with the use of cholinesterase inhibitors. This safety review was initiated when Health Canada learned that the European Medicines Agency had updated the product safety information related to this risk for 2 cholinesterase inhibitors (donepezil and galantamine).

At the time of review, the Canadian product monograph (CPM) for cholinesterase inhibitors included differing information about QT interval prolongation and/or torsade de pointes. The purpose of this review was to assess whether

additional warnings or other actions for QT interval prolongation and torsade de pointes were required in Canada.

Health Canada reviewed the available information from searches of the Canada Vigilance database, international databases and published literature. Health Canada reviewed 53 case reports (1 Canadian, 52 international) of QT interval prolongation and torsade de pointes in patients taking cholinesterase inhibitors. Of the 53 reports, 35 were for donepezil, 10 (1 Canadian) for galantamine, and 8 for rivastigmine. For donepezil, 2 cases were found to be probably linked, 30 cases were possibly linked, 2 cases were unlikely to be linked and 1 case could not be assessed. Four deaths were reported (2 of which were determined to have a possible link and 2 unlikely to be linked). For galantamine, 3 cases were found to be probably linked, 5 cases were possibly linked, 1 case was unlikely to be linked and 1 case (Canadian) could not be assessed. One death was reported and was unlikely to be linked. For rivastigmine, 7 cases were found to be possibly linked and 1 case was unlikely to be linked. Health Canada also reviewed 20 articles published in the scientific literature. There was limited evidence to support a link between the use of cholinesterase inhibitors and the risk of QT interval prolongation and torsade de pointes in these articles.

Health Canada's review supported a link between the use of all 3 cholinesterase inhibitors and the risk of QT interval prolongation and torsade de pointes, and determined that product information updates were warranted. Health Canada will work with the manufacturers of all cholinesterase inhibitors to strengthen the information in the CPMs about the risk of QT interval prolongation and torsade de pointes. This update will also advise that the risk is increased in patients with a history of certain heart conditions; a history or family history of QT interval prolongation; low levels of certain electrolytes, such as magnesium, potassium or calcium in the blood; or taking certain medications that can affect heart rhythm at the same time as the cholinesterase inhibitors.

In Hong Kong, there are registered pharmaceutical products containing donepezil (35 products), rivastigmine (30 products) and galantamine (10 products). All products are prescription-only medicines. As of the end of July 2022, the Department of Health (DH) had not received any case of adverse drug reaction related to donepezil. The DH had received adverse drug reactions related to rivastigmine (one case) and galantamine (one case), but these cases were not related to QT interval prolongation and torsade de pointes.

News related to cardiac conduction disorders (including QT interval prolongation and torsade de pointes) associated with the use of donepezil was previously issued by Australia Therapeutic Goods Administration, and was reported in Drug News Issue No. 148. In light of the above Health Canada's announcement, the DH issued letters to inform local healthcare professionals to draw their attention on 20 July 2022, and the matter will be discussed by the Registration Committee of the Pharmacy and Poisons Board.

The United Kingdom: Topiramate (Topamax): Start of safety review triggered by a study reporting an increased risk of neurodevelopmental disabilities in children with prenatal exposure

On 21 July 2022, Medicines and Healthcare products Regulatory Agency (MHRA) announced that it has initiated a new safety review into topiramate as a result of an observational study reporting an increased risk of neurodevelopmental disabilities in children whose mothers took topiramate during pregnancy. Topiramate is known to be associated with an increased risk of congenital malformations and effects on fetal growth if used during pregnancy. Healthcare professionals are advised to continue to counsel patients who can become pregnant on the known and emerging risks of topiramate for an unborn baby and on the need to use effective contraception throughout use.

A recently published study (Bjørk and colleagues) reported prenatal exposure to topiramate to be associated with an increased risk of autism and intellectual disability. The Commission on Human Medicines considered the findings of this new study and advised that it provides robust evidence to support an association between prenatal exposure to topiramate and an increased risk of autism spectrum disorder, intellectual disability and the composite outcome of any neurodevelopmental disorder. MHRA has now started a safety review to evaluate these findings in the context of the accumulating data relating to the benefits and risks of use of topiramate, with a particular focus on women of childbearing potential and during pregnancy. The review will also explore the need

for additional risk minimisation measures to reduce the potential harms associated with the use of topiramate during pregnancy.

While the review is ongoing, MHRA is alerting healthcare professionals to the findings of this new study and reminding them of the important risks and precautions to take when prescribing or dispensing topiramate in women of childbearing potential.

The study by Bjørk and colleagues is a large, well-conducted study using established data sources from 5 Nordic countries (Denmark, Finland, Iceland, Norway, and Sweden). It reports that children whose mothers use topiramate or valproate during pregnancy are at an increased risk of autism spectrum disorder, intellectual disability, and a composite outcome of any neurodevelopmental disorder. These risks are known for valproate.

Data from around 4.5 million mother-child pairs were examined and this included 24,825 children (0.6%) who were prenatally exposed to antiepileptic drugs. Of these, 16,170 were born to mothers who had epilepsy. These data were analysed to estimate the risk of autism spectrum disorder and intellectual disability after exposure to the 10 most frequently used antiepileptic drugs when used as monotherapy (one medicine) and the 5 most frequently used antiepileptic drugs when used as duotherapy (two medicines at the same time). In unexposed children of mothers with epilepsy, the 8-year cumulative incidence of autism spectrum disorder and intellectual disability were 1.5% and 0.8% respectively compared with 4.3% and 3.1% in children of mothers with epilepsy exposed to topiramate. The adjusted hazard ratios for autism spectrum disorder and intellectual disability were 2.8 (95% CI 1.4 to 5.7) and 3.5 (95% CI 1.4 to 8.6). A range of sensitivity analyses were conducted that broadly showed consistent and statistically significant effect estimates of a greater than 2-fold increase in risk of neurodevelopmental disorders across most of the analyses. The data also showed a dose-dependent effect for topiramate.

Before the initiation of topiramate in a woman of childbearing potential, pregnancy testing should be performed, and the patient should be fully informed of the risks if used during pregnancy. For epilepsy, alternative therapeutic options should be considered for women of childbearing potential. If topiramate is used, a highly effective contraception is strongly recommended, and the discussion with the patient should include information on both the risks associated with taking topiramate and of uncontrolled epilepsy during pregnancy. For migraine prophylaxis, topiramate is contraindicated in pregnancy and in women of childbearing potential if not using a highly effective method of contraception. As such, topiramate should not be prescribed for migraine prevention in a patient who is pregnant. Topiramate may reduce the effectiveness of steroidal contraceptives, including oral contraceptives. Alternative or concomitant methods of contraception should be considered.

Advice for healthcare professionals:

- MHRA has started a new safety review to assess the benefits and risks of topiramate and to consider whether further measures are required to reduce the risk of harm associated with topiramate use during pregnancy.
- The new safety review was triggered by a large observational study reporting that prenatal exposure to topiramate is associated with an increased risk of autism spectrum disorders, intellectual disability, and neurodevelopmental disorders.
- Of the antiepileptic medicines reviewed for use in pregnancy, lamotrigine and levetiracetam continue to be considered the safer for the baby since they were not associated with an increased risk of birth defects.
- It remains vital that the strict restrictions for valproate prescribing in women and girls of childbearing potential are followed given the known significant risks if valproate is used in pregnancy.
- Reminder of current advice for topiramate: do not prescribe topiramate during pregnancy for migraine prophylaxis; ensure any patients of childbearing potential know to use highly effective contraception throughout treatment with topiramate; counsel patients on the importance of avoiding pregnancy during topiramate use due to these emerging data and also the established increased risks of major congenital malformations and fetal growth restriction in babies exposed to topiramate in-utero; topiramate may reduce the effectiveness of steroidal contraceptives, including oral contraceptives, therefore consider alternative or concomitant methods; for migraine prophylaxis, topiramate can be withdrawn in pregnancy by an appropriate prescriber but alternative treatments should be considered;

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for epilepsy, urgently refer anyone on topiramate who is planning a pregnancy or who is pregnant for specialist advice on their antiepileptic treatment.

In Hong Kong, there are 32 registered pharmaceutical products containing topiramate. All products are prescription-only medicines. As of the end of July 2022, the Department of Health (DH) had received 4 cases of adverse drug reaction related to topiramate, but these cases were not related to neurodevelopmental disabilities in children with prenatal exposure. Related news was previously issued by European Medicines Agency, and the DH will remain vigilant on the conclusion of the review and any safety updates issued by other overseas drug regulatory authorities for consideration of any action deemed necessary.

Drug Recall

Further batch recall of Apo-Acyclovir Tablets 200mg and 800mg

Following the batch recall of the above two products, the Department of Health (DH) endorsed a licensed drug wholesaler, Hind Wing Co Ltd (Hind Wing), to further recall a total of three batches of the products from the market on 29 July 2022 as a precautionary measure due to the presence of an impurity in the products. Details of the affected batches are:

Name of product	Hong Kong registration number	Batch Number
Apo-Acyclovir Tablets 200mg	HK-43427	TF4466
Apo-Acyclovir Tablets 800mg	HK-58228	TE5062 TH6119

The DH received notification from Hind Wing on 29 July 2022 that the overseas manufacturer of the products is initiating a voluntary recall of the above batches due to the presence of a higher than accepted level of an impurity, N-nitrosodimethylamine (NDMA) in the affected batches.

NDMA is classified as a probable human carcinogen based on results from laboratory tests. As a precautionary measure, Hind Wing is voluntarily recalling the affected products from the market.

The above products are prescription medicines used for the treatment of herpes simplex. According to Hind Wing, the products have been imported into Hong Kong and supplied to local doctors, pharmacies and DH clinics.

As of the end of July 2022, the DH had not received any adverse reaction reports in connection with the products. A notice was posted on the Drug Office website on 29 July 2022 to alert the public of the product recall. The DH will closely monitor the recall.

A product containing any western drug ingredient must be registered under the Pharmacy and Poisons Ordinance before it can be sold in Hong Kong. Part 1 poisons should be sold at registered pharmacies under the supervision of registered pharmacists. Illegal sale or possession of Part 1 poisons and unregistered pharmaceutical products are offences under the Pharmacy and Poisons Ordinance (Cap. 138). The maximum penalty is a fine of $100,000 and two years' imprisonment for each offence. Antibiotics can only be supplied at registered pharmacies by registered pharmacists or under their supervision and upon a doctor's prescription. They should only be used under the advice of a doctor. Illegal sale or possession of antibiotics are offences under the Antibiotics Ordinance (Cap. 137) and the maximum penalty is a $50,000 fine and one year's imprisonment for each offence.

Under the Import and Export Ordinance (Cap. 60), pharmaceutical products must be imported or exported under and in accordance with an import or export licence issued under the Import and Export Ordinance. Illegal import or export of pharmaceutical products are offences under the Import and Export Ordinance (Cap. 60) and the maximum penalty is a fine of $500,000 and 2 years' imprisonment.

Update on Drug Office's website: You can now search the newly registered medicines in the past year at http://www.drugoffice.gov.hk/eps/drug/newsNRM60/en/healthcare_providers?pageNoRequested=1.
Details of ALL registered pharmaceutical products can still be found in the Drug Office website at http://www.drugoffice.gov.hk/eps/do/en/healthcare_providers/news_informations/reListRPP_index.html.

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The purpose of Drug News is to provide healthcare professionals with a summary of local and overseas drug safety news released. Healthcare professionals are advised to keep update with the information and provide corresponding advice or therapeutic measure to patients and public.