Drug News
藥 物 情 報

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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 2021 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

The United Kingdom: Chloramphenicol eye drops containing borax or boric acid buffers: use in children younger than 2 years

On 7 July 2021, Medicines and Healthcare products Regulatory Agency (MHRA) announced that chloramphenicol eye drops can be safely administered to children aged 0 to 2 years where antibiotic eye drop treatment is indicated.

In Oct 2017, warnings for boric acid (and borates) were introduced into the European Commission guideline for excipients in the labelling and package leaflet of medicines containing boron. Marketing authorisation holders were asked to update their product information (Summary of Product Characteristics and Patient information Leaflet) in line with the 2017 guidance over a period of time; and this occurred in the United Kingdom last year. The European guidance requires the addition of strong warnings not to give children aged 0 to 2 years products if an exposure greater than 1 milligram (mg) of boron a day is exceeded due to concerns around impaired fertility.

With restrictions introduced on the use of some products in children younger than 2 years, concerns were raised by the Royal College of Ophthalmologists and other professional organisations regarding the applicability of these warnings and restrictions for very young children and the lack of suitable alternatives to chloramphenicol eye drops. The MHRA therefore undertook a review of the interpretation of the European guidance on boric acid and borates as relates to children aged 0 to 2 years. The MHRA reviewed the available quality, clinical and toxicological evidence and sought independent expert advice from the Paediatric Medicines Expert Advisory Group of the Commission on Human Medicines to understand the risk for infants when these products are used within the licensed indication for what is likely to be a short period of time.

The European guidance threshold for boron is based on a pregnancy-related effect (reduced fetal weights). Furthermore, the uncertainty factors used in the derivation of the permitted daily exposure (PDE) are based on toxicokinetic and bodyweight data from pregnant rats and humans. Therefore, the MHRA's review concluded that the current PDE is not relevant to children aged 0 to 2 years. Based on studies conducted in animals, the most sensitive toxicological effect potentially relevant to infants is reproductive toxicity (adverse effects on fertility). This data was generated in adult animals, not juvenile animals, therefore the relevance to the developing reproductive tract and long-term effects on fertility are unknown. There are no data indicating clinical relevance to adults and children at present, therefore the assumption of potential risk to future fertility of infants is hypothetical. In terms of the exposures associated with the use of chloramphenicol eye drops, there are adequate safety margins in place for adverse effects on fertility and for exposures associated with reduced fetal weights, an endpoint not considered relevant to infants.

Levels of boron in chloramphenicol eye drops vary by product, but around 0.12mg of boron per drop might be present (based on a boron concentration of around 3mg/ml and a drop size of about 40 microlitres (µL). Boron exposure calculated using the full amount per drop appears to be an overestimate. Administering eye drops in young children is difficult due to lack of co-operation and potential crying during administration. Because of this, some liquid will be blinked out. Based on expert opinion, the maximum volume that can be accommodated in the conjunctival sac of a child

younger than 2 years is between 10µL and 20µL. Expert advice on current clinical practice suggests a typical regimen of one drop administered, applied typically 3 to 4 times a day to both eyes, which would result in a daily exposure well below 1mg per day, even if 100% absorption is assumed. For severe eye infections, the British National Formulary for Children (BNF-C) states a dose of one drop, every 2 hours (with frequency reduced as the infection is controlled). This would result in a daily exposure over the limit of 1mg per day threshold for infants younger than 2 years assuming the maximum dose (24 drops) is administered and 100% absorption occurs. Expert opinion is that it is unlikely that the maximum dose will be achieved as the drops will likely be only administered during waking hours and the high dose is for a short duration of a few days.

Given the toxicological data and the calculation of daily exposure from a typical dosing regimen, it has been concluded that the benefit-risk balance of chloramphenicol eye drops containing boron or boric acid remains positive for children aged 0 to 2 years.

The product information for affected chloramphenicol products will be updated shortly to reflect the revised advice that these products can be safely administered to children aged 0 to 2 years. The MHRA has requested the removal of restrictions and associated warnings about boron exposure in children aged 0 to 2 years from the product information for United Kingdom chloramphenicol eye drop products.

Advice for healthcare professionals:

- Some licences for chloramphenicol eye drop products containing borax or boric acid buffers were recently updated to restrict use in children younger than 2 years of age to reflect warnings on maximum daily limits for boron exposure.
- The MHRA has reviewed the available evidence and sought independent expert advice to understand whether there is a risk for children aged 0 to 2 years when using these products within the licensed indication, for what is likely to be a short period of time.
- The MHRA's review has concluded that the benefits of chloramphenicol eye drops containing borax or boric acid outweigh the potential risks for children, including those aged 0 to 2 years.
- A typical regimen of one drop, applied typically 3 to 4 times a day, to both eyes, would result in a daily exposure well below the safety limit for children aged 0 to 2 years.
- Advise parents and caregivers that chloramphenicol eye drops remain an important medicine for children when antibiotic eye treatment is indicated and that they have been used safely for many years.
- The product information for affected chloramphenicol products is being updated to reflect the revised advice and remove restrictions for use in infants, in the meantime the MHRA asks healthcare professionals to reassure parents and carers that these products can be safely given to children aged 0 to 2 years as prescribed.

In Hong Kong, there are 23 registered pharmaceutical products which are chloramphenicol-containing eye drops. All products are prescription-only medicines. Four of these products are indicated for children aged 2 years or above. For the remaining 19 products, they contain boric acid and related excipients. As of the end of July 2021, the DH has not received any case of adverse drug reaction related to chloramphenicol. Healthcare professionals are advised to balance the risk of possible adverse effects against the benefit of treatment.

The United States: Initial results of near real-time safety monitoring of COVID-19 vaccines in persons aged 65 years and older

On 12 July 2021, the US Food and Drug Administration (FDA) announced that it has routinely been using screening methods to monitor the safety of COVID-19 vaccines and to evaluate potential adverse events of interest (AEI) related to these vaccines. One of these methods, called near real-time surveillance, detected four potential AEIs in the Medicare healthcare claims database of persons aged 65 years and older who had received the Pfizer/BioNTech COVID-19 vaccine. The four potential AEIs are pulmonary embolism, acute myocardial infarction, immune thrombocytopenia, and disseminated intravascular coagulation. The screening methods have not identified these AEIs after vaccination in persons 65 years and older who received the two other authorized COVID-19 vaccines.

These four events may not be true safety concerns, and the screening method cannot establish that the vaccine caused these AEIs. FDA is sharing the

initial findings of this safety study in the spirit of transparency but does not believe there is a cause for concern. There are alternative explanations for the findings, including the fact that the Pfizer/BioNTech vaccine was given to many high-risk individuals who were older and had significant co-morbidities.

These events have not been identified as safety concerns or signals in the Centers for Disease Control and Prevention (CDC) Vaccine Safety Datalink (VSD) or the Veterans Administration (VA) Healthcare data systems screening methods. The Vaccine Adverse Event Reporting System (VAERS), another government monitoring system, also has not identified any association between any COVID-19 vaccine and these AEIs.

FDA continues to closely monitor the safety of the COVID-19 vaccines and will further investigate these findings by conducting more rigorous epidemiological studies. FDA will share further updates and information with the public as they become available. FDA strongly believes that the known and potential benefits of COVID-19 vaccination greatly outweigh the known and potential risks of COVID-19. There is no need to delay vaccination while the FDA continues its investigation.

In Hong Kong, the above product is not a registered pharmaceutical product under the Pharmacy and Poisons Ordinance (Cap. 138). The COVID-19 vaccine by Fosun Pharma/BioNTech (i.e. Comirnaty) is authorised for emergency use in Hong Kong in accordance with the Prevention and Control of Disease (Use of Vaccines) Regulation (Cap. 599K). The DH will remain vigilant on safety update of the product issued by other overseas drug regulatory authorities.

The United States: Statins: Drug Safety Communication - FDA Requests Removal of Strongest Warning Against Using Cholesterol-lowering Statins During Pregnancy

On 20 July 2021, the FDA announced that it is requesting revisions to the information about use in pregnancy in the prescribing information of the entire class of statin medicines. These changes include removing the contraindication against using these medicines in all pregnant patients. A contraindication is FDA's strongest warning and is only added when a medicine should not be used because the risk clearly outweighs any possible benefit. Because the benefits of statins may include prevention of serious or potentially fatal events in a small group of very high-risk pregnant patients, contraindicating these drugs in all pregnant women is not appropriate.

FDA expects removing the contraindication will enable health care professionals and patients to make individual decisions about benefit and risk, especially for those at very high risk of heart attack or stroke. This includes patients with homozygous familial hypercholesterolemia and those who have previously had a heart attack or stroke. Medicines in the statin class include atorvastatin, fluvastatin, lovastatin, pitavastatin, pravastatin, rosuvastatin, and simvastatin.

FDA also advises healthcare professionals that they should discontinue statin therapy in most pregnant patients, or they can consider the ongoing therapeutic needs of the individual patient, particularly those at very high risk for cardiovascular events during pregnancy. Because of the chronic nature of cardiovascular disease, treatment of hyperlipidemia is not generally necessary during pregnancy. Healthcare professionals should also discuss with patients whether to discontinue statins temporarily while breastfeeding. They should advise patients who require a statin because of their cardiovascular risk, that breastfeeding is not recommended because the medicine may pass into breast milk.

In Hong Kong, there are 286 registered pharmaceutical products containing statins (i.e. atorvastatin, fluvastatin, lovastatin, rosuvastatin, pravastatin, simvastatin) and they are all prescription-only medicines. As of the end of July 2021, the DH has received 27 cases of adverse drug reaction with statins, but none of them are related to pregnancy. The DH will remain vigilant on any further safety updates of statins issued by overseas drug regulatory authorities.

Australia: Methylphenidate: Use in pregnancy

On 22 July 2021, Therapeutic Goods Administration (TGA) announced that it is advising health professionals that the Product Information (PI) documents for methylphenidate products have been updated with new information about use in pregnancy. The pregnancy category has now been changed from Category B3 to Category D and the PI documents include updated safety information relating to birth defects and malformations.

Methylphenidate is a central nervous system stimulant. Its mode of action in humans is not completely understood, but methylphenidate presumably exerts its stimulant effect by an inhibition of dopamine and norepinephrine reuptake into presynaptic neurons and thereby increasing these neurotransmitters in the extraneuronal space.

The pregnancy category for methylphenidate was changed from pregnancy Category B3 to Category D due to a small increased occurrence of foetal cardiac malformations in women who received methylphenidate during the first trimester of pregnancy, compared with non-exposed pregnancies seen in large observational studies.

As at 4 Jun 2021, no cases of foetal cardiac malformations associated with methylphenidate had been reported to the TGA. However, the World Health Organization's global individual case safety report database, VigiBase, has received 28 reports of this adverse event.

Health professionals are advised that methylphenidate should not be prescribed for women of childbearing age unless, in the opinion of the physician, the potential benefits outweigh the possible risks.

In Hong Kong, there are 26 registered pharmaceutial products containing methylphenidate. All products are prescription-only medicines. As of the end of July 2021, the DH has received one case of adverse drug reaction related to methylphenidate, but this case is not related to birth defects. In light of the above TGA's announcement, the DH issued letters to inform local healthcare professionals to draw their attention on 23 July 2021, and the matter will be discussed by the Registration Committee of the Pharmacy and Poisons Board.

Australia: Pfizer COVID-19 vaccine (Comirnaty) - Addition of safety information about myocarditis and pericarditis to Product Information

On 23 July 2021, the TGA announced that the Product Information (PI) used by healthcare professionals for Comirnaty has been amended to include safety related information on myocarditis and pericarditis.

Myocarditis is inflammation of the heart muscle while pericarditis is inflammation of the lining around the heart. There are many potential causes of myocarditis and pericarditis, including as a complication in people who are infected with COVID-19 or some other viruses.

Very rare cases of myocarditis and pericarditis have been observed following vaccination with Comirnaty. These cases have primarily occurred within 14 days following vaccination, more often after the second vaccination, and more often in younger men. The changes to the Australian PI follow similar updates by the European Medicines Agency, Health Canada, the UK's Medicines and Healthcare products Regulatory Agency and the US Food and Drug Administration.

The benefits of protection against COVID-19 far outweigh the risks from rare and generally mild side effects. Effects on the heart from COVID-19 infection are much more common and usually more severe than with rare effects from vaccination. The Australian Technical Advisory Group on Immunisation (ATAGI) advises the Government on immunisation issues. ATAGI reaffirms that the benefits of Comirnaty outweigh these rare risks.

In Hong Kong, the above product is not registered pharmaceutical product under the Pharmacy and Poisons Ordinance (Cap. 138). The COVID-19 vaccine by Fosun Pharma/BioNTech (i.e. Comirnaty) is authorised for emergency use in Hong Kong in accordance with the Prevention and Control of Disease (Use of Vaccines) Regulation (Cap. 599K). The package insert of Comirnaty has already been updated to include myocarditis and pericarditis as its adverse reactions. Related news was previously issued by various overseas drug regulatory authorities. The DH issued letters to inform local healthcare professionals on 28 Jun 2021. The DH will remain vigilant on safety update of the product issued by other overseas drug regulatory authorities.

Drug Recall

Batch recall of Nucala Solution for Injection in Pre-filled Pen 100mg/ml

On 8 July 2021, the DH endorsed a licensed drug wholesaler, GlaxoSmithKline Limited (GSK), to recall a batch (batch number: 3K4D) of Nucala Solution for Injection in Pre-filled Pen 100mg/ml (Hong Kong Registration Number: HK-66838) from the market as a precautionary measure due to a potential quality defect of the product.

The DH received notification from GSK that a fibre was found in one of the finished products which is a quality defect. After assessment, the overseas manufacturer believes that the defect may be originated from a bulk product batch which may affect a number of finished product batches. As a result, the manufacturer decided to recall all the finished product batches. According to GSK, the batch 3K4D is the only affected batch which has been imported and supplied in Hong Kong. As a precautionary measure, GSK is voluntarily recalling the batch from the market.

The above product is a prescription medicine used for the treatment of severe asthma. According to GSK, the affected batch has been supplied to Hospital Authority, private hospitals and private doctors. As of the end of July 2021, the DH has not received any adverse reaction reports in connection with the batch of product. Press release was posted the Drug Office website on 8 July 2021 to alert the public of the product recall.

Drug Incident

Public urged not to buy or consume slimming products with undeclared controlled ingredients

On 23 July 2021, the DH appealed to the public not to buy or consume two slimming products named "温燃燒" and "消水丸" (no English names) as they were found to contain undeclared controlled drug ingredients.

Acting upon intelligence, samples of the above products were purchased earlier via a social media platform for analysis. Test results from the Government Laboratory revealed that the sample of "温燃燒" contained sibutramine and the sample of "消水丸" contained frusemide. Both ingredients are Part 1 poisons under the Pharmacy and Poisons Ordinance (Cap 138). The DH's investigation is continuing.

Sibutramine was once used as an appetite suppressant. Since November 2010, products containing sibutramine have been banned in Hong Kong because of an increased cardiovascular risk. Frusemide is a diuretic used in the treatment of high blood pressure, heart failure and oedema. Common adverse effects include feeling thirsty, dizziness, headaches and fast or irregular heartbeat.

Press release was posted on the Drug Office website on 23 July 2021 to alert the public of the drug incident.

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.

All registered pharmaceutical products should carry a Hong Kong registration number on the package in the format of "HK-XXXXX". The products mentioned in the above incidents were not registered pharmaceutical products under the Ordinance in Hong Kong. Their safety, quality and efficacy cannot be guaranteed. Members of the public were exhorted not to use products of unknown or doubtful composition. They should stop using the aforementioned products immediately if they had them in their possession and to consult healthcare professionals if they felt unwell after taking the products. The products should be destroyed or disposed properly, or submitted to the Department's Drug Office during office hours.

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.

Useful Contact

Drug Complaint:

Tel: 2572 2068
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E-mail: pharmgeneral@dh.gov.hk

Adverse Drug Reaction (ADR) Reporting:

Tel: 2319 2920
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E-mail: adr@dh.gov.hk
Link: http://www.drugoffice.gov.hk/adr.html

Post: Adverse Drug Reaction and Adverse Event Following Immunization Unit,
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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.