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 December 2016 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

EU: European Medicines Agency to review certain injectable medicines to treat allergy - Risks of some methylprednisolone products in patients allergic to cows' milk proteins to be investigated

On 2 December 2016, the European Medicines Agency (EMA) announced that it has started a review of certain medicines given by injection to treat severe, rapidly developing (acute) allergic reactions. The medicines involved contain the corticosteroid methylprednisolone as active ingredient. They also include as an additional ingredient lactose (milk sugar), which potentially contains traces of cows' milk proteins that could affect treatment of acute reactions in the small number of highly sensitive patients allergic to these proteins.

The review is triggered by reports of patients treated for allergic conditions with these medicines, who were also allergic to cows' milk proteins. The medicine itself apparently caused an allergic reaction in these patients. In such circumstances, the reaction to the medicine may be mistaken for a worsening of the original condition, leading to additional doses of the medicine being given.

EMA will evaluate the available data on the risk of an allergic reaction to the medicine itself, and consider whether there is a need for measures to minimize the risk. The scope of the review has been limited to these allergy medicines where patients may be more sensitive and confusion between the condition and the reaction to the medicine can lead to incorrect treatment. However, it is expected that any findings from the review will contribute to work that is already ongoing to improve information for patients and doctors about all medicines that contain lactose as an additional ingredient.

Allergy to cows' milk protein affects a small percentage of the population (around 2 to 50 people in 1000) and should not be confused with lactose intolerance which is a separate condition.

In Hong Kong, there are eight registered pharmaceutical products containing methylprednisolone for injection. Amongst them, only one product Solu Medrol 40mg Steril Mix-O/Act-O Vial (HK-00466) contains both methylprednisolone and lactose, and the product is registered by Pfizer Corporation Hong Kong Limited and is a prescription only medicine. As on 27 February 2017, the Department of Health (DH) has received four adverse drug reaction (ADR) cases related to methylprednisolone for injection but none of the ADR case was related to allergic reactions. DH will continue to remain vigilant on the outcome of the EMA review and on further safety updates on methylprednisolone and lactose issued by other overseas drug regulatory authorities.

Australia: Phenytoin (Dilantin) bottles of capsules and tablets: Recall for product correction - Child-resistant caps may not function correctly

On 6 December 2016, the Australia Therapeutic Goods Administration (TGA) advised consumers and healthcare professionals that Pfizer Australia, in consultation with TGA, has initiated a recall for product correction for bottles of phenytoin 30 mg capsules, 100 mg capsules and 50 mg tablets, which are marketed under the brand name Dilantin.

Dilantin is an anticonvulsant used to control epilepsy.

It has been identified that bottles of Dilantin may have been supplied with child-resistant caps that may not engage or otherwise be properly secured. This creates a potential risk that a child could open a bottle and access the medicine. To correct this issue, Pfizer Australia has initiated a recall for product correction to replace all bottles of Dilantin which have child-resistant caps that do not engage or otherwise are not properly secured. Pfizer Australia has written to doctors providing further information about this issue, including a patient communication letter.

Doctors in Australia are advised that if they are treating a patient who is taking Dilantin, contact patients either by phone or with the patient communication letter within the following three weeks to advise them of this issue. Pharmacists in Australia are advised that before dispensing new prescriptions for Dilantin or replacing returned bottles, check to ensure that the child-resistant cap is functioning correctly. Any bottle with a child-resistant cap that is not functioning correctly should be returned to Pfizer Australia. Doctors and pharmacists should reassure patients that there is no other concern regarding the quality or safety of these

medicines, but consider reminding them of the importance of keeping all medicines out of the reach of children.

In Hong Kong, the pharmaceutical products Dilantin Cap 30 mg (HK-07922) and 100 mg (HK-07909) are registered by Pfizer Corporation Hong Kong Limited (Pfizer HK), and are prescription only medicines. As confirmed with Pfizer HK, only Dilantin Cap 30 mg marketed in Hong Kong is originated from the same Australian manufacturer and is packaged in bottles with child-resistant caps. Majority of Dilantin Cap 30 mg is supplied to Hospital Authority (HA), and the remaining is supplied to private hospitals, doctors and pharmacies. Pfizer HK has notified HA about the incident. So far up to 7 December 2016, the company has received one case of defective bottle cap requiring product replacement. Pfizer HK has requested its distributor to check the bottle caps of the product before distribution, and would notify private hospitals, doctors and pharmacies about the incident. DH will continue to remain vigilant on the development of the incident.

UK: Cobicistat, ritonavir and co-administration with a steroid: Risk of systemic corticosteroid adverse effects

On 14 December 2016, the Medicines and Healthcare products Regulatory Agency (MHRA) advised that co-administration of a corticosteroid with an HIV-treatment-boosting agent may increase the risk of adrenal suppression due to a pharmacokinetic interaction.

Pharmacokinetic boosters are agents used in inhibiting the metabolism of other substances, thereby increasing or prolonging the action of these substances. Ritonavir and its structural analogue cobicistat, being inhibitors of the CYP3A subfamily, are boosting agents that prolong the action of some antiretroviral medicines.

Corticosteroids are mainly metabolised by the CYP3A enzyme group, particularly CYP3A4. Therefore, the use of a CYP3A inhibitor with a corticosteroid is anticipated to increase the systemic steroid levels.

For cobicistat, an European Union (EU)-wide review has identified 8 cases worldwide (including 1 published report) of adrenal suppression during treatment with a cobicistat-containing regimen (Stribild) and subsequent prescription of an inhaled, intranasal, or intra-articular corticosteroid. Reported reactions were adrenal insufficiency, adrenal suppression, and Cushing's syndrome. The corticosteroids involved were intranasal and inhaled fluticasone, oral budesonide, and intra-articular triamcinolone. From clinical trials, a further report of adrenal insufficiency was identified where epidural methylprednisolone had been used together with intranasal fluticasone. Most reports involved long-term use of corticosteroids, ranging from 9 months to over 1 year – also a known risk factor for the development of adrenal suppression.

Product information for cobicistat-containing products in the United Kingdom (UK) is being strengthened to: warn the potential of systemic corticosteroid-related reactions occurring with concomitant use; highlight the need for monitoring of patients for these events during treatment; and advise the consideration of lower-risk alternatives where possible (particularly, inhaled or intranasal beclomethasone).

Beclomethasone is less dependent on CYP3A metabolism than some other corticosteroids, and in general, interactions are unlikely. However, the possibility of systemic effects with concomitant use of cobicistat cannot be excluded, and therefore, caution and appropriate monitoring are still advised with the use of beclomethasone.

Product information for corticosteroids in UK is also being updated to warn the potential for the interactions, resulting in systemic corticosteroid-related effects. This update excludes, however, formulations intended for cutaneous use only because of limited evidence of an interaction with cobicistat.

For ritonavir, reports of corticosteroid-related effects have been received concerning patients taking HIV-protease inhibitors boosted with ritonavir who were also given epidural, intra-articular, or intramuscular injections of triamcinolone. Up to 21 November 2016, 26 UK Yellow Card reports of an interaction with triamcinolone and ritonavir have been reported: 18 reactions of Cushing's syndrome or cushingoid features, and 17 reactions of adrenal suppression. Product information for injectable formulations containing triamcinolone is being updated in UK to warn the interaction with ritonavir.

A separate EU review identified 2 reports of Cushing's syndrome from interactions between ocular dexamethasone and ritonavir. The review also noted an increased risk of systemic adrenal effects occurring with both ocular and cutaneous use after intensive or long-term therapy, and also considered these factors to be a risk for interactions with ritonavir. Product information for dexamethasone ocular and cutaneous formulations is being updated in UK with warnings about the potential interaction with CYP3A4 inhibitors, including ritonavir; warnings are already present in the product information for dexamethasone in UK administered via oral or parenteral routes.

MHRA advised healthcare professionals of the followings:

- all clinicians who may prescribe or administer steroids to patients with HIV should be aware that concomitant use of a corticosteroid metabolised by cytochrome P450 3A (CYP3A) and a HIV-treatment-boosting agent may increase the risk of systemic corticosteroid-related adverse effects
- although these reactions are rarely reported, there is potential for this interaction to occur even with non-systemically administered steroid formulations, including intranasal, inhaled, and intra-articular routes
- co-administration of a HIV-treatment-boosting agent with a CYP3A-metabolised corticosteroid is not recommended unless the potential benefit to the patient outweighs the risk, in which case, the patients should be monitored for systemic corticosteroid-related reactions
- if co-administration is necessary, use of beclomethasone should be considered where possible – particularly for long-term use. Beclomethasone is less

dependent on CYP3A metabolism and, although the risk of an interaction leading to adverse corticosteroid effects may not be removed completely, it may be lower

In Hong Kong, there are four registered pharmaceutical products containing cobicistat for HIV infection, namely Stribild Tablets (HK-62550), Stribild Tablets (HK-64384), Genvoya Tablets (HK-64455) and Prezcobix Tablets 800mg/150mg (HK-64960); and there are four registered pharmaceutical products containing ritonavir for HIV infection, namely Kaletra Oral Sol (HK-48165), Kaletra Tab (HK-55200), Kaletra Tab 100mg/25mg (HK-58310) and Norvir Tablet 100mg (HK-61528). All these eight products are prescription only medicines. As on 27 February 2017, DH has not received any ADR report related to co-administration of cobicistat with a corticosteroid, or co-administration of ritonavir with a corticosteroid. In view of the MHRA announcement, DH issued a letter to inform local healthcare professionals on the warnings on 15 December 2016, and the matter would be discussed by the Registration Committee of the Pharmacy and Poisons Board.

US: Chantix (varenicline) and Zyban (bupropion): Mental health side effects revised

On 16 December 2016, the United States (US) Food and Drug Administration (FDA) announced FDA reviewed a large clinical trial that the administration had required the drug companies to conduct, and determined that the risk of serious side effects on mood, behavior, or thinking with the stop-smoking medicines Chantix (varenicline) and Zyban (bupropion) is lower than previously suspected.

As a result of the review, FDA is removing the Boxed Warning, the FDA's most prominent warning, for serious mental health side effects from the Chantix label. The language describing the serious mental health side effects seen in patients quitting smoking will also be removed from the Boxed Warning in the Zyban label. FDA is also updating the existing warning section in both labels that describes the side effects on mood, behavior, or thinking to include the results from the clinical trial. The patient Medication Guide that explains the risks associated with the use of the medicines will continue to be provided in US with every patient prescription; however, the risk evaluation and mitigation strategy (REMS) that formally required the Medication Guide will be removed.

In Hong Kong, there are three registered pharmaceutical products containing varenicline, namely Champix Tab 0.5mg (HK-55479), Champix Tab 0.5mg & 1mg (HK-55462) and Champix Tab 1mg (HK-55437), and there are five registered pharmaceutical products containing bupropion, namely Zyban Sustained-Release Tab 150mg (HK-46946), Wellbutrin SR Sustained-Release Tab 150mg (HK-52125), Wellbutrin XL Extended Release Tab 300mg (HK-58253), Wellbutrin XL Extended Release Tab 150mg (HK-58371) and PMS-Bupropion SR Tab 150mg (HK-58534). All eight products are prescription only medicines. Related news about the risk of psychiatric symptoms on varenicline issued previously by the Australia TGA and US FDA was reported in Drug News Issue No. 65. In view of the previous FDA announcement, DH issued a letter to inform local healthcare professionals on the warnings on 10 March 2015. DH will continue to remain vigilant on further safety updates of varenicline and bupropion issued by other drug regulatory authorities.

Singapore: Fluoroquinolones and the potential risk of retinal detachment

On 20 December 2016, Singapore Health Sciences Authority (HSA) issued an announcement on the potential risk of retinal detachment associated with the use of oral fluoroquinolones. Fluoroquinolones are broad-spectrum antibiotics that are used to treat a wide range of indications such as infections of the urinary tract, respiratory tract, skin and soft tissue, bones and joints, and abdominal cavity. Oral fluoroquinolones licensed in Singapore include ciprofloxacin, levofloxacin, moxifloxacin, norfloxacin, pefloxacin, ofloxacin, and lomefloxacin.

The association between oral fluoroquinolones intake and occurrence of retinal detachment has been investigated in several epidemiological studies. Two large cohort studies have found a statistically significant increased risk of retinal detachment associated with the use of oral fluoroquinolones.

This increased risk of retinal detachment was not confirmed in other published studies as well as in a study conducted by EMA. However, in most of these studies, the confidence intervals were relatively wide and thus a small increase in risk cannot be excluded.

EMA and Health Canada have reviewed this safety concern. Both agencies concluded that a causal relationship between fluoroquinolones intake and retinal detachment cannot be excluded based on the available data. Given the seriousness of retinal detachment with possible sequelae and the need for immediate intervention by an ophthalmologist in the event when this occurs, both EMA and Health Canada have recommended the package inserts of fluoroquinolones to highlight the urgency to consult a healthcare professional if patients experienced vision problems during or following oral fluoroquinolones administration.

HSA has not received any reports of retinal detachment associated with the use of fluoroquinolones although HSA has received several reports describing visual disturbances such as blurred vision, eye redness, itching and conjunctivitis.

HSA has been working with the drug companies to update the package inserts of fluoroquinolone-containing products registered in Singapore on the warning of this potential risk and to highlight the need to seek medical attention in the event of visual impairment and disturbances. In view of the fact that retinal detachment is serious and that its association with oral fluoroquinolones use cannot be ruled out, healthcare professionals are advised to consider this potential risk when prescribing and dispensing fluoroquinolones to patients.

In Hong Kong, there are 248 registered pharmaceutical products containing fluoroquinolones, including 106 ciprofloxacin, 67 levofloxacin, 52 ofloxacin, 8 moxifloxacin,

11 norfloxacin, 2 lomefloxacin, 1 prulifloxacin and 1 sparfloxacin products. All these products are prescription only medicines. As on 27 February 2017, DH has received two ADR cases after receiving levofloxacin, and they are not related to retinal detachment, and no ADR case has been received for the remaining fluoroquinolones. In light of the reviews by EMA, Health Canada and HSA, DH issued a letter to inform local healthcare professionals on the warnings on 21 December 2016, and the matter would be discussed by the Registration Committee of the Pharmacy and Poisons Board.

Canada: Health Canada reviewing potential negative effects of general anesthetics and sedatives on young children and fetuses

On 22 December 2016, Health Canada announced that it was reviewing the safety of certain drugs used for general anesthesia and sedation in children under the age of three, or in pregnant women during their third trimester. This follows a recent communication by US FDA warning the public that repeated or lengthy use of general anesthetics and sedatives in these groups may have potential negative effects on the development of children's brains.

"General" anesthetics and sedatives are administered by highly trained specialists in healthcare settings so that the patient is unconscious and does not feel pain during surgery, procedures or tests. General anesthetics are usually given by injection into a vein, or inhaled. The risk being communicated does not involve "local" or "regional" anesthetics, which are used to numb specific areas or regions of the body.

As noted in FDA communication, studies in young animals have shown that anesthetics can be harmful to the developing brain. Some studies of children who have undergone anesthesia suggest that there may be long-term effects on learning and behaviour, while other studies have not shown a link. It is difficult to know whether these effects were due to the drugs or other reasons, such as the medical condition for which the anesthesia was needed. According to FDA, recent human studies suggest that a single, relatively short exposure to general anesthetics and sedatives in infants or toddlers is unlikely to have negative effects on behaviour or learning.

Health Canada is currently reviewing this safety issue and collaborating with other foreign agencies. Health Canada is assessing all available information, including scientific literature and new international developments, to determine whether the current labelling accurately reflects the scientific knowledge that has been obtained from animal studies.

Health Canada will continue to update Canadians, including healthcare professionals, as the review is completed, and will take action, as needed, to optimize the benefits and reduce the risks associated with anesthetics and sedatives in children and pregnant women.

Anesthetics and sedatives are essential to preventing pain during surgery and other procedures or tests. They play a vital role in critical and sometimes life-saving procedures that should not be delayed. When making any decisions on the necessity and timing of a procedure, healthcare professionals and patients should weigh the risks and benefits. Pregnant women, parents and caregivers should discuss any questions or concerns about the use of sedatives, general anesthesia and/or the necessity of a procedure with their healthcare professionals.

In Hong Kong, there are 30 registered pharmaceutical products containing general anaesthetic and sedative drugs as stated in the FDA and Health Canada announcements, including 1 desflurane, 5 isoflurane, 4 sevoflurane, 1 etomidate, 5 ketamine, 7 midazolam injection, 1 pentobarbital, and 6 propofol products. Related news was previously issued by FDA. DH issued a letter to inform local healthcare professionals on the warnings on 15 December 2016. As on 27 February 2017, DH has not received any ADR report related to negative effects on behaviour and learning in young children and pregnant women after using the above drugs, and the matter would be discussed by the Registration Committee of the Pharmacy and Poisons Board.

Advice to Healthcare Professionals

Adherence to the recommended rate of infusion of INTRATECT (Human Immunoglobulin)

On 20 December 2016, DH issued a letter to healthcare professionals concerning the recommended rate of infusion when administering INTRATECT, an immunoglobulin product, especially in paediatric patients.

As recommended in the product information of Intratect Solution for Infusion 2.5g/50ml (HK-61283) and Intratect Solution for Infusion 5g/100ml (HK-61287), an initial rate of no more than 1.4ml/kg/h for 30 minutes must not be exceeded during the infusion. If well tolerated, the rate of administration may gradually be increased to a maximum of 1.9ml/kg/h for the remainder of infusion.

The appeal follows the review of ADR Reporting System database which has identified 2 paediatric cases of chills and rigors. Both cases were suspected to be related to the administration of Intratect at an infusion rate which exceeded the recommendations of the product information.

In Hong Kong, there are other registered pharmaceutical products containing human normal immunoglobulin which may have different recommended infusion rate. Healthcare professionals are advised to check the instructions in the product information carefully before administration.

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 $30,000 fine and one year's imprisonment for each offence.

Latest update on the Drug Office's website: You can now search the new registered medicines in the past year at the following Drug Office website:
http://www.drugoffice.gov.hk/eps/drug/newsNRM60/en/pharmaceutical_trade?pageNoRequested=1.
Details of ALL the registered medicines can also be found at the following Drug Office website:
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.