Drug News
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Issue Number 48

This is a monthly digest of local and overseas drug safety news released by the Drug Office of the Department of Health in October 2013 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

Singapore: Contraindication of the subcutaneous administration of Eprex® (epoetin alfa) in chronic kidney disease patients

Subsequent to the notice dated 13 June 2013 from the Health Sciences Authority (HSA), about an increase in the number of erythropoietin antibody-mediated pure red cell aplasia (PRCA) cases with onset in 2012 and 2013 observed from one institution in Singapore, the HSA informed healthcare professionals on 2 October 2013 that the subcutaneous (SC) administration of Eprex® is contraindicated in all chronic kidney disease (CKD) patients including end stage renal disease (ESRD) patients. A strong association of antibody-mediated pure red cell aplasia (PRCA) with SC administration of Eprex® was observed from local reports. Thus, a decision was made following HSA's benefit-risk assessment in consultation with an expert panel, comprising renal physicians and haematologists, that the benefit-risk profile of Eprex® when administered subcutaneously, was no longer favourable in CKD patients. Healthcare professionals are advised that CKD patients who are currently receiving SC Eprex® should be reviewed as soon as possible so that they can switch to IV Eprex® or consider other therapeutic options. They are also advised to continue to closely monitor their patients for antibody-mediated PRCA when using all erythropoeisis stimulating agents (ESAs) and to remind patients on the importance and use of appropriate travel pack to maintain recommended storage temperatures during the transportation of the ESAs.

In Hong Kong, there are 13 registered pharmaceutical products containing epoetin alfa. They are prescription only medicines indicated for the treatment of anaemia and can be administrated intravenously or subcutaneously. News regarding PRCA case cluster observed with SC administration of Eprex® released by HSA was reported in Drug News Issue No. 44. The Department of Health (DH) had not received any adverse reaction report in connection with epoetin alfa. In view of HSA's latest recommendation, a letter to healthcare professionals was issued on 4 October 2013, and the matter will be discussed in the meeting of the Pharmacy and Poisons (Registration of Pharmaceutical Products and Substances: Certificate of Clinical Trial/Medicine Test) Committee (the Registration Committee) of the Pharmacy and Poisons Board.

Singapore: Durogesic® (fentanyl) Transdermal System and Fentanyl Injection 0.1mg/2ml (fentanyl citrate) may be associated with serotonin syndrome under co-administration with serotonergic drugs

It was noted from HSA website on 8 October 2013 that Janssen, a division of Johnson & Johnson Pte Ltd, alerted healthcare professionals to the possibility of serotonin syndrome, a potentially life -threatening condition, when serotonergic drugs are administered concomitantly with the fentanyl-containing products, including Durogesic® Transdermal System and Fentanyl Injection 0.1mg/2ml. Based on the results and conclusions of the company's review, caution should be taken when these products are co-administered with drugs that affect serotonergic neurotransmitter systems. Serotonin syndrome is not an adverse drug reaction associated with the use of Durogesic® or Fentanyl Injection alone, but may occur with the

concomitant use of drugs such as Selective Serotonin Re-Uptake Inhibitors (SSRIs), Serotonin Norepinephrine Re-Uptake Inhibitors (SNRIs) and Monoamine Oxidase Inhibitors (MAOIs). If serotonin syndrome is suspected, treatment with Durogesic® or Fentanyl Injection should be discontinued.

In Hong Kong, there are five pharmaceutical products containing fentanyl registered by Johnson & Johnson (Hong Kong) Ltd (Johnson & Johnson), namely Fentanyl Inj 0.005% (HK-08700), Durogesic Transdermal Patch 12mcg/h (HK-53883), 25mcg/h (HK-53755), 50mcg/h (HK-53753) and 100mcg/h (HK-53754). All of them are prescription only medicines indicated for the treatment of chronic pain. Johnson & Johnson issued Dear Healthcare Professional letters for Fentanyl Inj and Durogesic Transdermal Patch regarding the above safety concern on 15 October and 18 November 2013 respectively. The current inserts of the products have included the warning on the relevant safety information. DH will keep vigilant on any safety updates of the products.

EU / UK: The benefits of combined hormonal contraceptives continue to outweigh risks

Subsequent to the previous announcement by the European Medicines Agency (EMA) in January that its Pharmacovigilance Risk Assessment Committee (PRAC) would review the newer generations combined hormonal contraceptives (CHCs) to assess whether the currently available product information provided the best information possible for patients and doctors, the EMA announced on 11 October 2013 that its PRAC concluded that the benefits of CHCs in preventing unwanted pregnancies continue to outweigh their risks. The PRAC reviewed the risk of venous thromboembolism (VTE) with CHCs and confirmed that the risk of VTE with all CHCs is small and the small differences in risk among CHCs depended on the type of progestogen that they contain. Having assessed all the available data, the PRAC concluded that:

- The risk is lowest with the CHCs containing levonorgestrel, norgestimate and norethisterone: it is estimated that each year there will be between 5 and 7 cases of VTE per 10,000 women who use these medicines.
- The risk is estimated to be higher with etonogestrel and norelgestromin, with between 6 and 12 cases yearly per 10,000 women.
- The risk is also estimated to be higher with gestodene, desogestrel, drospirenone, with between 9 and 12 cases yearly per 10,000 women.
- For CHCs containing chlormadinone, dienogest and nomegestrol, the available data are insufficient to know how the risk compares with the other CHCs, but further studies are ongoing or planned.
- For comparison, in women who are not using CHCs and who are not pregnant, there will be around 2 cases of VTE each year per 10,000 women.

The review also looked at the risk of arterial thromboembolism. This risk is very low and there is no evidence for a difference in the level of risk between products depending on the type of progestogen. When prescribing a CHC, healthcare professionals are advised to assess a woman's individual risk for blood clots regularly, as the risk changes over time. Risk factors include smoking, being overweight, increasing age, having migraines, family history of VTE and having given birth in the previous few weeks.

The Medicines and Healthcare Products Regulatory Agency (MHRA) of the United Kingdom (UK) followed EMA's recommendation, and advised that patients on these medicines should continue to take their contraceptive pills.

In Hong Kong, there are 26 registered pharmaceutical products which are combined oral contraceptives. The types of progestogen that they contain include levonorgestrel, norethisterone, gestodene, desogestrel, drospirenone and dienogest. The concerns related to the risk of VTE of the CHCs that released by EMA was reported in Drug News Issue No. 39. DH will keep vigilance on any safety updates of the drugs and actions taken by overseas regulatory authorities for consideration of any action deemed necessary.

EU: Latest recommendation on the use of Hydroxyethyl-starch solutions

On 14 June 2013, the EMA's PRAC concluded that the benefits of infusion solutions containing hydroxyethyl-starch (HES) were no longer outweigh their risks and therefore recommended that the marketing authorisations for these medicines be suspended. On 11 October 2013, the EMA announced that the PRAC had completed its review of HES solutions following an assessment of new information and looked at the new proposals from manufacturers of additional risk minimisation measures. The PRAC now confirmed that HES solutions must no longer be used to treat patients with sepsis (bacterial infection in the blood) or burn injuries or critically ill patients, because of an increased risk of kidney injury and mortality. HES solutions may, however, continue to be used in patients to treat hypovolaemia caused by acute blood loss, where treatment with alternative infusions solutions known as 'crystalloids' alone are not considered to be sufficient. The PRAC acknowledged the need for measures to minimise potential risks in these patients and recommended that HES solutions should not be used for more than 24 hours and that patients' kidney function should be monitored for at least 90 days. In addition, the PRAC requested that further studies be carried out on the use of these medicines in elective surgery and trauma patients. EMA announced on 25 October 2013 that the above PRAC recommendations were endorsed by the Coordination Group for Mutual Recognition and Decentralised Procedures – Human and the decision would send to the European Commission to take it legally binding.

In Hong Kong, there are six registered pharmaceutical products containing HES, namely Voluven Infusion 6% (HK-50474), Volulyte 6% Solution for Infusion (HK-58087), Tetraspan 6% Solution for Infusion (HK-56978), Tetraspan 10% Solution for Infusion (HK-56979), Hestar-200 Inj. 10% (HK-57095) and Hestar-200 Inj. 6% (HK-57096). Only 2 products, Voluven Infusion 6% and Volulyte 6% Solution for Infusion which are registered by Fresenius Kabi Hong Kong Ltd., are marketed in Hong Kong. They are indicated for the therapy and prophylaxis of hypovolaemia. Related news released by EMA, the US Food and Drug Administration (FDA), Health Canada and MHRA were reported in Drug News Issue No. 44. A letter to healthcare professionals was issued on 17 June 2013. The Registration Committee discussed the matter at its latest meeting in July 2013 and, based on the available evidences, concluded that DH will remain vigilant on any further new safety updates of HES released by overseas regulatory authorities for future consideration by the Registration Committee. This latest recommendation from EMA will be brought forward to Registration Committee for further consideration.

Canada: New heart warnings for the drug Sensipar (cinacalcet)

On 15 October 2013, Health Canada announced about a possible link between Sensipar (cinacalcet) and abnormal heart rhythm associated with low blood calcium. Stronger warnings were added to the drug label to inform the patients about the risk of QT prolongation and arrhythmia associated with the use of Sensipar and to advise healthcare professionals to monitor and report heart-related side effects.

Sensipar is well known to cause hypocalcemia, which can cause QT prolongation and arrhythmia. QT prolongation and arrhythmia had been reported in a small number of patients with hypocalcemia treated with Sensipar. It is difficult to determine with certainty what role Sensipar may have played in the development of QT prolongation or arrhythmia, as other risk factors were present at the same time. However, given the effect of hypocalcemia on the heart, the possibility of developing QT prolongation or arrhythmia with the use of Sensipar could not be ruled out.

Health professionals are advised to monitor patients for signs of hypocalcemia, and prescribe Sensipar with caution in patients with other risk factors for QT prolongation, such as known congenital long QT syndrome, or in patients who are taking other drugs known to cause QT prolongation. For patients treated with Sensipar for chronic kidney disease and receiving dialysis, reduce dose or stop use if hypocalcemia, signs of QT prolongation, or arrhythmia continue. For these patients, Sensipar should not be started if they have severe hypocalcemia.

In Hong Kong, there are two registered pharmaceutical products containing cinacalcet, namely Regpara Tab 25mg (HK-58066) and Regpara Tab 75mg (HK-58067). They are prescription only medicines indicated for secondary hyperparathyroidism in adult patients undergoing maintenance dialysis. The DH had not received any adverse drug reaction report in relation to the drug. In view of Health Canada's latest recommendations, a letter to healthcare professionals was issued on 16 October 2013 and the matter will be discussed in the meeting of the Registration Committee.

Canada: Updated labelling information for Acetylsalicylic Acid products

On 17 October 2013, Health Canada released an update labelling requirement for acetylsalicylic acid (ASA) containing products for use in adults and children aged 12 years and older. Outer and inner labels of all ASA containing products will be required to have warning statements that include the following:

1. KEEP OUT OF THE REACH OF CHILDREN.
2. DO NOT take more than the recommended dose unless advised by your doctor. Use the smallest effective dose.
3. DO NOT TAKE if you are in your last trimester of pregnancy.
4. DO NOT GIVE to children and teenagers less than 18 years of age who have chicken pox, cold or flu symptoms before a physician or pharmacist is consulted about Reye's Syndrome, a rare serious illness reported to be associated with acetylsalicylic acid.

Codeine or caffeine warnings are also required for products that contain codeine or caffeine in addition to ASA. This includes a new warning that nursing mothers should not take ASA products that contain codeine as codeine my cause serious harm to a breastfed baby.

In Hong Kong, there are 36 registered pharmaceutical products containing aspirin (acetylsalicylic acid). According to the "Guidelines on the Labelling of Pharmaceutical Products", products containing aspirin must be labelled with (on the label and/or package insert) —

1. Keep out of reach of children. This medicine should not be given to children under 16 except on medical advice.
2. Consult your physician before taking aspirin during pregnancy or when nursing.
3. Aspirin irritates the stomach and can cause bleeding. It should not be taken by patients with stomach ulcers, persistent indigestion or liver disease.

DH will keep vigilant on any safety updates of the drug and actions taken by other overseas regulatory authorities for consideration of any action deemed necessary.

The Mainland: Allopurinol tablets associated with serious drug rash

On 18 October 2013, the China Food and Drug Administration (CFDA) alerted public on the risk of serious drug rash associated with allopurinol tablets. In the year 2012, the National Centre for Adverse Drug Reaction (ADR) Monitoring of China received 485 cases of ADRs related to allopurinol tablets, among them 140 were severe cases. The top three ADRs were events associated with skin, events associated with gastrointestinal systems, and anaphylactic shock, which accounted for 81.11% of all cases. The main event associated with skin was serious drug rash, such as exfoliative rashes (24 cases), erythema multiforme (6 cases) and toxic epidermal necrolysis (1 case). After the analysis of these reports, the CFDA recommended that:

- ◊ when allopurinol tablet is prescribed, healthcare professionals should pay attention to the dosage adjustments in special populations and the contraindications, and avoid off-label use. In addition, allopurinol tablet should be used with caution in patients with history of hypersensitive and allergy. Be cautious when co-administered with other medicines to avoid any drug interactions. Treatment should be discontinued and medical intervention be sought immediately when the patient is presented with any skin allergy or other severe allergic reactions.
- ◊ the pharmaceutical manufacturers are advised to revise the product inserts, to strengthen the post-marketing ADR monitoring and actively

carry out quality and technology research. Meanwhile, they should also strengthen public health protection by means of promoting the safe use of the medicine via training and rational drug use.

In Hong Kong, there are 44 registered tablets containing allopurinol. All of them are pharmacy only medicines indicated for the treatment of gout. DH will keep vigilant on any safety updates of the drug released by other regulatory authorities.

EU: Restrictions on use of short-acting beta-agonists in obstetric indications

On 25 October 2013, the EMA announced that the new recommendations to restrict the use of short-acting beta-agonists had been endorsed by the Coordination Group for Mutual Recognition and Decentralised Procedures – Human. These medicines should no longer be used in oral or suppository forms in obstetric indications, such as for suppressing premature labour or excessive labour contractions. However, injectable forms of these medicines can still be given for short-term obstetric use under specific conditions.

These recommendations follow a review of available cardiovascular safety data on the medicines fenoterol, hexoprenaline, isoxsuprine, ritodrine, salbutamol and terbutaline when used in obstetric indications by the PRAC. Given the cardiovascular risk and the very limited data on the effectiveness of the oral and suppository forms of these medicines, the PRAC concluded that their benefit-risk balance is not favourable and these medicines should no longer be used in obstetric indications.

In addition to oral medicines and suppositories, this review also covered injectable short-acting beta-agonists used as tocolytics. The PRAC concluded that the benefits of injectable forms of these medicines continue to outweigh their risks when used under specific conditions including:

- ◊ to suppress premature labour for up to 48 hours;
- ◊ between the 22nd and the 37th weeks of pregnancy; and
- ◊ under specialist supervision with continuous monitoring of the mother and the unborn baby.

In countries where injectable forms are also authorised for external cephalic version and emergency use in specific conditions, the PRAC recommended that they remain authorised in these indications. It proposed revising their prescribing information, with reinforced warnings on the cardiovascular risks.

In Hong Kong, there are 82 registered pharmaceutical products containing fenoterol, hexoprenaline, ritodrine, salbutamol and terbutaline in oral dose form and 4 registered pharmaceutical products containing hexoprenaline, ritodrine, salbutamol and terbutaline in injectable form. In view of EMA's recommendations, a letter to healthcare professionals was issued on 28 October 2013 and the matter will be discussed in the meeting of the Registration Committee.

Drug Recall

Recall of 塔牌腰痛大補丹

On 31 October 2013, DH instructed a licensed drug wholesaler, Hong Kong Han Lam Tong Medicine Limited (Han Lam Tong), to recall a health product, namely 塔牌腰痛大補丹 from shelves due to quality issue.

Under the DH's market surveillance, sample of the product was found to have contained trace amount of an undeclared antimicrobial, ciprofloxacin. The product is promoted for use in lubricating the joint and strengthening the bone. DH had closely monitored the recall. A press statement was released on the same day to alert the public of the recall.

Members of the public who have purchased the above product should stop using it immediately. People who are feeling unwell or in doubt after using the product should consult healthcare professionals.

Public urged not to buy or use oral product labelled as OxyELITE Pro

On 9 October 2013, DH appealed to members of the public not to buy or consume an oral product labelled as OxyELITE Pro, as it may have linked to some cases of acute non-viral hepatitis in Hawaii of the US.

Through the DH's drug surveillance system, it is noted that FDA had advised consumers to stop using a dietary supplement product labelled as OxyELITE Pro which may have related to cases of acute non-viral hepatitis in Hawaii. Among the 29 cases reported so far, eleven cases had been hospitalised, two cases had received liver transplants and one person died. Twenty-four of the cases shared a common link to OxyELITE Pro. According to FDA, the product was distributed by USPlabs LLC in the US. The joint investigation conducted by the US authorities continues. FDA is also investigating whether counterfeit product is related to any of the cases of acute hepatitis.

In Hong Kong, OxyELITE Pro is neither a registered pharmaceutical product nor registered proprietary Chinese medicine. The DH had previously received a report concerning a female suffering from acute hepatitis symptoms after consuming an oral product labelled as OxyELITE Pro and the product remnant was found to contain an undeclared Western drug ingredient, yohimbine, which is a Part I poison used in the treatment of orthostatic hypotension. Its side effects include increase in heart rate and blood pressure, anxiety, manic reactions and bronchospasm. Products containing yohimbine can only be sold in a pharmacy under the supervision of a registered pharmacist. A press release was issued on 5 June 2013 accordingly.

Members of public are urged not to buy or consume unregistered pharmaceutical products as they have not been evaluated by the Pharmacy and Poisons Board and their safety, quality and efficacy are not guaranteed.

Woman arrested for suspected illegal sale of Part I Poison on the Internet

On October 28 2013, a joint operation was conducted by DH and the Police in Mong Kok for illegal sale of Iressa, a medicine containing a Part I poison.

During the DH's surveillance programme, it was found that the above product was offered for sale on an Internet auction site. The seller was arrested by the Police for illegal sale of a Part I poison during the operation.

Iressa, containing the Part I poison Gefitinib, is indicated for the treatment of non-small-cell lung cancer. The product is a prescription drug which should only be used under the direction of a medical practitioner. It can only be sold at a pharmacy under the supervision of a registered pharmacist with a doctor's prescription.

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 I poisons should be sold at registered pharmacies under the supervision of registered pharmacists. Illegal sale or possession of Part I 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.

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.

Useful Contact

Drug Complaint:

Tel: 2572 2068
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Adverse Drug Reaction (ADR) Reporting:

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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.