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 January 2014 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: Advisory on the use of cyproterone acetate/ethinylestradiol

It was noted from the website of Health Sciences Authority (HSA) on 4 January 2014 that new restrictions would be imposed to limit the use of products containing cyproterone acetate/ ethinylestradiol (CPA/EE) so as to mitigate the risks of venous and arterial thromboembolism in view of the modest benefit derived from treatment with CPA/EE for conditions such as androgenetic alopecia and mild acne. And the local package inserts would be strengthened as follows:

- CPA/EE is indicated for the treatment of moderate to severe acne related to androgen-s ensitivity (with or without seborrhoea) and/or mild forms of hirsutism in women of reproductive age
- When used for the treatment of acne, CPA/EE should only be used after topical therapy or systemic antibiotic treatments have failed
- CPA/EE is no longer indicated for the treatment of androgenetic alopecia
- CPA/EE should not be prescribed for the purpose of contraception alone
- The need to continue treatment should be evaluated periodically by the treating physician
- The use of CPA/EE carries an increased risk of VTE compared with no use. The excess risk of VTE is highest during the first year a women starts CPA/EE or when restarting or switching after a pill-free interval of at least a month

In Hong Kong, there are ten registered products containing CPA and EE, including the brand Diane -35 Tab (HK-43330). All are prescription only medicines indicated for the treatment of severe acne and moderately severe hirsutism. Safety alerts on CPA/EE had been released by various regulatory authorities which had been reported in Drug News Issue 39 and 43. 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 had already discussed the issue in July 2013 and decided that in order to ensure the safe use of pharmaceutical products containing the combination of CPA and EE, the sales pack labels and/or package inserts of combination products containing CPA and EE should be revised as follows:

A. *to remove the indication of "androgenetic alopecia";*

B. *to include new safety information for "indications". Examples of the wordings are:*

- *although this product also acts as an oral contraceptive, it should not be used in women solely for contraception, but should be reserved for those women requiring treatment for androgen-dependent conditions only, i.e. moderately severe hirsutism and severe acne;*
- *this product should only be used for the treatment of acne when alternative treatments, e.g. topical therapy and oral antibiotic treatment, have failed; and*

C. *to include new information for "warnings". Examples of the wordings are:*

- *there is some epidemiological evidence that the incidence of venous thromboembolism is higher in users of this product when compared to users of combined oral contraceptives with low oestrogen content (<50mcg ethinylestradiol).*
- *This product is contraindicated in women with thrombophlebitis, thromboembolic disorders, or a history of these conditions.*

US: Possible harm from exceeding recommended dose of over-the-counter sodium phosphate products to treat constipation

On 8 January 2014, the Food and Drug Administration (FDA) of the United States (US) warned healthcare professionals about the risk of rare but serious harm to the kidneys and the heart, and even death for products containing sodium phosphate if the recommended dose is exceeded. Sodium phosphate drug products include oral solutions taken by mouth and enemas used rectally, and are indicated for the relief of occasional constipation, and for bowel cleansing before rectal examinations.

FDA received reports of severe dehydration and changes in serum electrolytes levels from taking more than the recommended dose of sodium phosphate products, resulting in serious adverse effects on organs, such as the kidneys and heart, and in some cases resulting in death. These serum electrolytes include calcium, sodium, and phosphate. Most reported cases of serious harm occurred with a single dose of sodium phosphate that was larger than recommended or with more than one dose in a day. Some individuals may be at higher risk for potential adverse events when the recommended dose of sodium phosphate is exceeded. These include young children; those older than 55 years; patients who are dehydrated; patients with kidney disease, bowel obstruction, or inflammation of the bowel; and patients who are using medications that may affect kidney function. These medications include diuretics, angiotensin converting enzyme inhibitors, angiotensin receptor blockers and nonsteroidal anti-inflammatory drugs.

Healthcare professionals are advised to use these products as recommended on the label, and not exceed the labeled dose. Healthcare professionals are also advised to use the products with caution when recommending such oral products for children 5 years and younger, and that the rectal form of these products should never be given to children younger than 2 years.

In Hong Kong, there are four registered pharmaceutical products containing sodium phosphate, of which three products are enemas and one is oral solution. All the products are non-poisons and can be purchased over-the-counter. The Department of Health (DH) had not received any adverse reaction report in connection with the drug. In view of FDA's finding, a letter to healthcare profesionals was issued on 9 January 2014 and the matter will be discussed in the meeting of the Registration Committee.

EU: Recommendation to suspend the use of Protelos/Osseor (strontium ranelate)

Further to the recommendation on restricting the use of strontium ranelate to reduce the risk of heart problems made by the European Medicines Agency (EMA) on 11 April 2013, the EMA's Pharmacovigilance Risk Assessment Committee (PRAC) had recommended on 10 January 2014 that Protelos/Osseor (strontium ranelate) should no longer be used to treat osteoporosis.

PRAC had conducted an in-depth review taking into account available data on the benefits and risks of the medicine. The Committee noted that for every 1,000 patients being treated for 1 year, there were 4 more cases of serious heart problems (including heart attacks) and 4 more cases of blood clots or blockages of blood vessels with Protelos/ Osseor than with placebo. In addition, Protelos/ Osseor is associated with a number of other risks, such as serious skin reactions, disturbances in consciousness, seizures (fits), liver inflammation and reduced number of blood cells. The Committee also questioned the evidence on the extent to which the restrictions recommended in April 2013 reduced the cardiovascular risk and how well the restrictions work in clinical practice, particularly as the medicine is used for long-term treatment in elderly patients. Besides, with regard to its benefits, Protelos/Osseor had been shown to

have a modest effect in osteoporosis, preventing about 5 non-spinal fractures, 15 new spinal fractures and 0.4 hip fractures for every 1,000 patients being treated for 1 year. PRAC weighed the benefits of the medicine against the known risks and concluded that the balance was no longer favourable and recommended Protelos/Osseor be suspended until there are new data showing a favourable balance in a defined patient group. The outcome of PRAC's assessment was sent to the EMA's Committee for Medicinal Products for Human Use (CHMP) for a final opinion.

In the meeting in February 2014, CHMP agreed with the PRAC's overall assessment of the risks of Protelos/Osseor, but noted that study data showed a beneficial effect in preventing fractures, including in patients at high risk of fracture and available data did not show evidence of an increased cardiovascular risk with Protelos/Osseor in patients who did not have a history of heart or circulatory problems. CHMP concluded that Protelos/Osseor remain available but recommended further restricting the use of the medicine to patients who cannot be treated with other medicines approved for osteoporosis. In addition, these patients should be screened and monitored regularly, every 6 to 12 months and treatment should be stopped if patients develop heart or circulatory problems.

In Hong Kong, Protos Granules for Oral Suspension 2g (HK-53835) containing strontium ranelate is registered by Servier HK Ltd. It is a prescription only medicine used for the treatment of severe osteoporosis in postmenopausal women at high risk for fracture to reduce the risk of vertebral and hip fractures. Safety alerts on the risks of venous thromboembolism and severe skin reactions were reported in Drug News Issues No. 23, 25, 29 and 41. The issues were discussed in the meeting of the Registration Committee in February 2013. The Registration Committee decided that the sales pack or package insert should be updated to include the appropriate safety information as stated in Drug News Issue No. 41. Safety alert on the risk of cardiovascular events was reported in Drug News Issue No. 42. A letter to healthcare professionals regarding the recommendation to restrict use of strontium ranelate made by EMA was issued on 15 April 2013. In connection with the above reported risks, the Registration Committee had discussed the matter in September 2013 and decided that the sales pack or package insert should be updated to include the following safety information:

A. *<u>Indications</u>:*

- *Treatment of severe osteoporosis in postmenopausal women at high risk for fracture to reduce the risk of vertebral and hip fractures*
- *The decision to prescribe strontium ranelate should be based on an assessment of the individual patient's overall risks*

B. *<u>Contraindications:</u>*

- *Established, current or past history of ischaemic heart disease, peripheral arterial disease and/or cerebrovascular disease.*
- *Uncontrolled hypertension.*

C. *<u>Posology</u>:*

- *Treatment should only be initiated by a physician with experience in the treatment of osteoporosis.*

D. *<u>Special warnings and precautions for use</u>:*

- *In pooled randomized placebo-controlled studies of post-menopausal osteoporotic patients, a significant increase in myocardial infarction has been observed in [brand name] treated patients compared to placebo.*
- *Before starting treatment and at regular intervals, patients should be evaluated with respect to cardiovascular risk.*
- *Patients with significant risk factors for cardiovascular events (e.g. hypertension, hyperlipidaemia, diabetes mellitus, smoking) should only be treated with strontium ranelate after careful consideration.*
- *Treatment should be stopped if the patient develops ischaemic heart disease, peripheral arterial disease, cerebrovascular disease or if hypertension is uncontrolled.*

In view of PRAC's recommendation to suspend the use of strontium ranelate and the final recommendation made by CHMP to remain the drug available but with further restrictions, the matter

will be discussed in the meeting of the Registration Committee. DH will remain vigilant on any safety updates of the drug.

Canada: Potential for medication errors during preparation of Jevtana (cabazitaxel) leading to overdose

On 10 January 2014, Health Canada informed healthcare professionals about the potential for medication errors leading to overdose in the preparation of Jevtana® (cabazitaxel), and the importance of ensuring that the entire content of the diluent is added to the concentrate vial during reconstitution. Reconstitution errors with Jevtana® (cabazitaxel) had been reported in Europe that led to overdoses 15% to 20% higher than the prescribed dose, although cases of reconstitution errors had not been reported in Canada. Errors in the administered dose occurred in the first step of the reconstitution where only the nominal volume of the diluent vial (4.5 mL) was transferred to the concentrate vial, instead of the entire content (5.67 mL). This resulted in a more concentrated premix, leading to a higher dose of Jevtana® delivered.

Pharmacies are advised to review worksheets used in the preparation of cabazitaxel to ensure that they instruct pharmacy staff to add the entire content of the diluent vial to the concentrate. Where an automated software system is used to prepare the infusion solution, the system must be set up to allow withdrawal of the entire content of the diluent vial to add to the concentrate vial. The anticipated complications of overdose include exacerbation of adverse reactions such as bone marrow suppression and gastrointestinal disorders. The local package insert of Jevtana® is being updated to improve the clarity of the dilution instructions.

In Hong Kong, there is one registered pharmaceutical product Jevtana Concentrate and Solvent for Solution for Infusion 6mg (HK-61193) containing cabazitaxel. It is a prescription only medicine indicated with prednisone or prednisolone for the treatment of patients with hormone refractory metastatic prostate cancer previously treated with a docetaxel-containing regimen and registered by Sanofi-Aventis Hong Kong Limited (Sanofi-Aventis). Sanofi-Aventis had issued a Direct Healthcare Professional Communication to remind and reiterate the right preparation instruction of Jevtana to Hospital Pharmacists and Oncologists in Hong Kong, and submitted the application to change the package insert of Jevtana by including the above safety information regarding the appropriate preparation of the product. DH will remain vigilant on any safety updates of the drug.

Canada: Effient (prasugrel hydrochloride) associated with increased risk of bleeding in patients treated in hospital for certain types of heart attacks

On 17 January 2014, Health Canada informed healthcare professionals of important safety information about Effient® (prasugrel hydrochloride), an antiplatelet agent indicated for the prevention of atherothrombotic events in patients with acute coronary syndromes.

A recent study (ACCOAST) showed an increased risk of bleeding with the use of half loading dose (30 mg) of Effient® prior to coronary angiography followed by the second half loading dose (30mg) at the time of percutaneous coronary intervention (PCI) compared to taking the full approved loading dose (60 mg) at the time of PCI. The information concerns the indication related to unstable angina (UA) or non-ST-segment elevation myocardial infarction (NSTEMI).

Health Canada advised that in UA/NSTEMI patients, when coronary angiography is performed within 48 hours after admission, the 60mg loading dose of Effient® should generally be given at the time of PCI in order to minimize the risk of bleeding, followed by a 10 mg maintenance dose.

In Hong Kong, there are two pharmaceutical products namely Effient Tab 5mg (HK-59090) and Effient Tab 10mg (HK-59091) containing prasugrel. They are prescription only medicines indicated for the prevention of atherothrombotic events in patients with acute coronary syndromes. In view of Health Canada's recommendation, a letter to healthcare professionals was issued on 20 January 2014. The Registration Committee had discussed the matter in February 2014 and decided that the package inserts of the products should be updated to include the following safety information:

"A recent study (ACCOAST) showed an increased

risk of bleeding with the use of half loading dose (30 mg) of EFFIENT® prior to coronary angiography followed by the second half loading dose (30mg) at the time of PCI compared to taking the full approved loading dose (60 mg) at the time of PCI."

Drug Incident

Woman arrested for suspected trafficking in dangerous drug

On 9 January 2014, a joint operation was conducted by DH and the Police in Kwun Tong resulting in the arrest of a 26-year-old woman for suspected illegal sale of a product named "Duromine Capsules 30mg", labelled as containing a dangerous drug substance.

Upon the investigation of a public complaint, DH found that the above product was offered for sale through a mobile phone communication application. "Duromine Capsules 30mg" is labelled as containing phentermine, which is a substance controlled under the Dangerous Drug Ordinance (Cap 134). Phentermine is used for the short term treatment of moderate to severe obesity. Side effects include tachycardia, palpitations and hypertension. It is also a prescription drug which should only be used under the direction of a medical practitioner. It can only be sold at a pharmacy by a registered pharmacist or under his supervision upon a doctor's prescription.

Members of the public are urged not to buy or consume products of unknown or doubtful composition or from unknown sources. A press statement was released on the same day to alert the public of the incident.

Retail shops raided for suspected illegal sale and possession of unregistered pharmacaeutical products and possession of unregistered proprietary Chinese medicines

On 16 January 2014, a joint operation was conducted by DH and the Police against three retail shops in Mong Kok area in the arrest of three women and two men aged between 19 to 60 for suspected illegal sale and possession of unregistered pharmaceutical products and suspected possession of unregistered proprietary Chinese medicines (pCms).

Acting on intelligence, DH found various suspected unregistered pharmaceutical products and pCms being offered for sale by the three retail shops. The seized products include eyedrop, antacid, cold and flu medicine and pain killer, were labelled in Japanese. Preliminary information indicated that some were labelled as containing Part I poisons such as ibuprofen, dihydrocodeine and neostigmine; and some were labelled as containing herbal medicines. According to DH's record, they were not registered pharmaceutical products or pCms and Hong Kong registration numbers for pharmaceutical products or for pCms were not found on any of the product labels. Preliminary investigation had so far revealed that the products were sourced outside Hong Kong.

Use of unregistered pharmaceutical products or pCms may pose health threats to people as their safety, efficacy and quality may not be guaranteed. In addition, inappropriate use of painkillers like ibuprofen without medical supervision may lead to gastrointestinal bleeding, and products with the ingredients dihydrocodeine and neostigmine may cause nausea and vomiting. Members of the public should not self-medicate without advice from healthcare professionals. A press statement was released on the same day to alert the public of the incident.

Retail shop raided for illegal sale of slimming product with banned drug ingredient

On 29 January 2014, a joint operation was conducted by DH and the Police resulting in the arrest of a 33-year-old woman for selling a slimming product named "Slim fast" which is suspected to contain an undeclared and banned drug substance.

During the DH's surveillance programme, a sample of the product concerned was obtained from the retail shop for analysis. Analytical results from the

Government Laboratory revealed that the slimming product contains phenolphthalein, a banned drug ingredient. During the operation, other capsules of different colours with the same packing label "Slim fast" were also found. All were seized for further analysis. Phenolphthalein was used previously to treat constipation, but has been banned for its cancer -causing effect. A press statement was released on the same day to alert the public of the 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 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. Trafficking in dangerous drugs is a criminal offence under the Dangerous Drugs Ordinance (Cap 134) and the maximum penalty is a $5,000,000 fine and life imprisonment upon conviction.

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.

With regard to the regulatory control of proprietary Chinese medicines, you can visit www.cmchk.org.hk for more details.

Useful Contact

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