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 November 2015 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

Canada: Safety information for antipsychotic drug "Abilify" and risk of certain impulse-control behaviours

On 2 November 2015, Health Canada announced that labels for the prescription antipsychotic drugs Abilify and Abilify Maintena (aripiprazole) have been updated to advise of an increased risk of impulsive behaviours of pathological gambling and hypersexuality.

Abilify, a tablet taken by mouth, is authorized to treat a certain type of bipolar disorder (bipolar, a serious manic-depressive illness involving extreme manic or mixed episodes) in adults and adolescents aged 13 years and older. It is also authorized to treat schizophrenia and related severe psychotic disorders in patients aged 15 years and older, and Major Depressive Disorder in adults when used in combination with other drugs. Abilify Maintena is an injectable drug administered by health professionals and is used to treat schizophrenia in adults.

The Canadian Product Monograph revisions are the result of a Health Canada safety review that found an increased risk of two types of impulsive behaviours with the use of these drugs: 18 international cases of pathological (uncontrollable) gambling, and six international cases of hypersexuality (uncontrollable and/or inappropriate sexual thoughts, urges or behaviours that are so severe or last so long that they cause distress).

These drugs are widely prescribed, with millions of prescriptions dispensed worldwide each year. They play an important role in helping patients manage serious psychiatric illness and their benefits as an effective treatment option are considered to outweigh their risks. Prior to the review, Abilify Maintena included information on reports of hypersexuality. The label updates help further clarify what is known about these drugs with respect to these rare risks, and add new warnings.

In Hong Kong, there are 10 registered pharmaceutical products containing aripiprazole under the brand names of Abilify (6 oral and 1 injectable products) and Aripiprazole Sandoz (3 oral products). The former 7 products are registered by Otsuka Pharmaceutical (HK) Ltd, while the latter 3 products are registered by Novartis Pharmaceuticals (HK) Limited. All products are prescription-only medicines. As on 23 December 2015, the Department of Health (DH) has not received any adverse drug reaction (ADR) case related to aripiprazole. In view of the warnings in the Health Canada's announcement, the DH issued a letter to inform local healthcare professionals of the advice on 3 November 2015. The matter will be discussed by the Registration Committee of the Pharmacy and Poisons Board.

EU: Review concludes evidence does not support that HPV vaccines cause CRPS or POTS

On 5 November 2015, the European Medicines Agency's (EMA) Pharmacovigilance Risk Assessment Committee (PRAC) has completed a detailed scientific review of the evidence surrounding reports of two syndromes, complex regional pain syndrome (CRPS) and postural orthostatic tachycardia syndrome (POTS) in young women given human papillomavirus (HPV)

vaccines. These vaccines are given to protect them from cervical cancer and other HPV-related cancers and pre-cancerous conditions. This review concluded that the evidence does not support a causal link between the vaccines (Cervarix, Gardasil/Silgard and Gardasil-9) and development of CRPS or POTS. Therefore, there is no reason to change the way the vaccines are used or amend the current product information.

CRPS is a chronic pain syndrome affecting a limb, while POTS is a condition where the heart rate increases abnormally on sitting or standing up, together with symptoms such as dizziness, fainting and weakness, as well as headache, aches and pains, nausea and fatigue. In some patients they can severely affect the quality of life. The syndromes are recognised to occur in the general population, including adolescents, regardless of vaccination.

Symptoms of CRPS and POTS may overlap with other conditions, making diagnosis difficult in both the general population and vaccinated individuals. However, available estimates suggest that in the general population around 150 girls and young women per million aged 10 to 19 years may develop CRPS each year, and at least 150 girls and young women per million may develop POTS each year. The review found no evidence that the overall rates of these syndromes in vaccinated girls were different from expected rates in these age groups, even taking into account possible underreporting. The PRAC noted that some symptoms of CRPS and POTS may overlap with chronic fatigue syndrome (CFS, also known as myalgic encephalomyelitis or ME). Many of the reports considered in the review have features of CFS and some patients had diagnoses of both POTS and CFS. Results of a large published study that showed no link between HPV vaccine and CFS were therefore particularly relevant.

In Hong Kong, there are three registered pharmaceutical products of human papillomavirus (HPV) vaccine, namely Gardasil Vaccine Inj (Vial) (HK-54934) and Gardasil Vaccine Inj (Pre-filled Syringe) (HK-54935) registered by Merck Sharp & Dohme (Asia) Ltd; and Cervarix Vaccine (Pre-filled Syringe) (HK-56180) registered by GlaxoSmithKline Limited. All products are prescription-only medicines. Related news on the start of scientific review on HPV vaccines was released by the EMA and was reported on the Drug News Issue No. 69. As on 23 December 2015, the DH has received 11 cases of ADRs following immunization of HPV, and none of them was related to CRPS and/or POTS. In view of the conclusions of the scientific review by the EMA, the DH issued a letter to inform local healthcare professionals on 6 November 2015. The DH will continue to remain vigilant on the safety of HPV vaccines.

US: FDA review finds long-term treatment with blood-thinning medicine Plavix (clopidogrel) does not change risk of death

On 6 November 2015, a US Food and Drug Administration (FDA) review has determined that long-term use of the blood-thinning drug Plavix (clopidogrel) does not increase or decrease overall risk of death in patients with, or at risk for, heart disease. FDA's evaluation of the Dual Antiplatelet Therapy (DAPT) trial and several other clinical trials also does not suggest that clopidogrel increases the risk of cancer or death from cancer.

In order to investigate the increased risk of death and cancer-related death reported with clopidogrel in the DAPT trial, FDA examined the results of the DAPT trial and other large, long-term clinical trials of clopidogrel with data available on rates of death, death from cancer, or cancer reported as an adverse event. FDA performed meta-analyses of other long-term clinical trials to assess the effects of clopidogrel on death rates from all causes. The results indicate that long-term (12 months or longer) dual antiplatelet therapy with clopidogrel and aspirin do not appear to change the overall risk of death when compared to short-term (6 months or less) clopidogrel and aspirin, or aspirin alone. Also, there was no apparent increase in the risks of cancer-related deaths or cancer-related adverse events with long-term treatment.

FDA is working with the manufacturers of clopidogrel to update the label to reflect the results of the mortality meta-analysis.

Healthcare professionals are encourage to advise patients to report any unanticipated, prolonged, or excessive bleeding, or blood in their stools or urine. When selecting antiplatelet therapy for patients with an acute coronary syndrome who are managed

with coronary stent implantation, prescribers should consider that prasugrel and ticagrelor have been shown to be superior to clopidogrel when used in this patient population. In addition, in patients with a history of myocardial infarction one to three years prior to study enrollment, ticagrelor has also been shown to reduce the risk of cardiovascular death, myocardial infarction, and stroke.

In Hong Kong, there are 32 registered pharmaceutical products containing clopidogrel, and are prescription-only medicines. As on 23 December 2015, the DH has received notification of two ADR cases after taking clopidogrel, but they were not related to cancer or cancer-related death. In view of the above conclusions of the scientific review by the FDA, the DH issued a letter to inform local healthcare professionals on 9 November 2015. The DH will continue to remain vigilant on the safety of clopidogrel.

UK: Crizotinib (Xalkori): risk of cardiac failure

On 12 November 2015, the Medicines and Healthcare products Regulatory Agency (MHRA) announced that there have been reports of severe, sometimes fatal, cases of cardiac failure in patients treated with crizotinib. A review by European medicines regulators of data from clinical trials and reports from clinical practice has concluded that this side effect is common (i.e. occurs in between 1 in 10 and 1 in 100 patients who take crizotinib).

Crizotinib (Xalkori) is licensed to treat adults with previously treated anaplastic lymphoma kinase (ALK)-positive advanced non-small-cell lung cancer.

Up to 25 February 2015, about 14,700 patients worldwide have received crizotinib since licensing. Forty cases of cardiac failure have been reported in the post-marketing setting. In most cases cardiac failure occurred within 1 month of starting treatment with crizotinib, and affected patients with or without pre-existing heart disorders. The reports included some cases with evidence of symptoms of cardiac failure resolving on stopping crizotinib, and cases with evidence of symptoms reoccurring when it was reintroduced.

In the UK, the MHRA has received 2 Yellow Card reports of suspected heart failure with crizotinib up to 3 November 2015, 1 of which was fatal.

The MHRA advises healthcare professionals of the following:

- Monitor all patients for signs and symptoms of heart failure (including dyspnoea, oedema, or rapid weight gain from fluid retention)
- Consider reducing the dose, or interrupting or stopping treatment if symptoms of heart failure occur

In Hong Kong, there are two pharmaceutical products containing crizotinib, namely Xalkori Cap 200mg (HK-61969) and 250mg (HK-61968) registered by Pfizer Corporation Hong Kong Limited (Pfizer HK). They are prescription-only medicines and their package inserts do not have warnings on cardiac failure. As on 23 December 2015, the DH has received four ADR cases related to crizotinib, and none of them was related to cardiac failure. In view of the MHRA announcement, the DH issued a letter to inform local healthcare professionals on 13 November 2015. The matter will be discussed by the Registration Committee of the Pharmacy and Poisons Board.

UK: Vemurafenib (Zelboraf): risk of potentiation of radiation toxicity

On 12 November 2015, the MHRA announced a review of worldwide data by EU medicines regulators concluded that vemurafenib can potentiate radiation toxicity. In phase III and phase IV clinical trials, approximately 1 in 20 patients who received vemurafenib had a radiation-related injury, either radiation recall or radiation sensitisation.

Vemurafenib (Zelboraf) is indicated as monotherapy for the treatment of adults with BRAF V600 mutation-positive unresectable or metastatic melanoma.

These cases occurred in patients who received radiation before, during, or after treatment with vemurafenib. Most cases were confined to the skin, but some involved visceral organs and resulted in a fatal outcome (including one case of radiation necrosis of the liver and two cases of radiation

oesophagitis). Most patients had received doses of radiation ≥2 Gy/day.

Cases of radiation recall were confined to the previously irradiated area. Most cases (5 of 8) affected the skin, although 2 cases involved the lung and 1 case the bladder. Skin reactions included: eczematous, vesicular, or ulcerative lesions; erythema; and hyperkeratosis. Mean time to onset of radiation recall after vemurafenib initial dose was 12 days (range 7–21) for skin reactions, 24 days for pneumonitis; and 1 day for cystitis.

Most cases of radiation sensitisation (9 of 12) involved the skin, although there has been a case each involving the oesophagus, liver, and rectum. The nature of skin radiation sensitisation was similar to that seen in radiation recall skin reactions. Except for one case, vemurafenib was given concomitantly with radiation or within 3 days after completion of radiotherapy. When reported, the mean time to onset of the reaction after initiation of radiotherapy or vemurafenib was 10 days (range 3–27).

Up to October 2015, the MHRA has received 2 UK Yellow Card reports of radiation injury and related events in patients receiving vemurafenib.

In Hong Kong, there is one pharmaceutical product containing vemurafenib, namely Zelboraf Film-coated Tab 240mg (HK-61970) registered by Roche Hong Kong Limited (Roche HK), and is a prescription-only medicine. As on 23 December 2015, the DH has not received any ADR case related to vemurafenib. Roche HK has already applied to include the new warnings in the local package insert and is under process. In view of the MHRA announcement, the DH issued a letter to inform local healthcare professionals on 13 November 2015. The DH will continue to remain vigilant on the safety of vemurafenib.

US: FDA advises of rare cases of underactive thyroid in infants given iodine-containing contrast agents for medical imaging

On 17 November 2015, the US FDA was advising that rare cases of underactive thyroid have been reported in infants following the use of contrast media containing iodine, also called "contrast dye" for X-rays and other medical imaging procedures. In all of the reported cases, the infants were either premature or had other serious underlying medical conditions. Available evidence leads FDA to believe that this rare occurrence is usually temporary and resolves without treatment or any lasting effects.

Parents and caregivers should contact their baby's healthcare professionals for additional information or if they have questions or concerns about their baby receiving an iodinated contrast media (ICM) product. Infants typically do not show any visible signs of underactive thyroid. The thyroid is a gland in the neck that releases hormones. Healthcare professionals should continue to follow the label recommendations for ICM products. They should continue to use their clinical judgment to determine if testing for underactive thyroid is necessary.

ICM are drugs containing iodine that are given to patients to enhance the ability to see blood vessels and organs on medical images such as X-rays or computed tomography (CT) scans. These images provide greater detail when necessary to help healthcare professionals diagnose potential problems.

A search of the FDA Adverse Event Reporting System (FAERS) database identified 10 cases of underactive thyroid reported between 1969 and early 2012 in infants younger than 4 months who received ICM. FAERS includes only reports submitted to FDA, so there may be additional cases about which FDA is unaware. In addition to ICM, several of these infants also received a topical iodine product that is no longer recommended for young infants, and that may have contributed to their underactive thyroids. All of the infants were diagnosed with underactive thyroid within a month of receiving ICM. Some infants were treated and improved while others improved without treatment.

In Hong Kong, there are 15 registered pharmaceutical products which are ICM products under the brand names of Visipaque containing iodixanol (2 products), Omnipaque containing iohexol (2 products), Iopamiro containing iopamidol (4 products), Ultravist containing iopromide (2 products), Optiray containing ioversol (4 products) and Hexabrix containing meglumine ioxaglate and sodium ioxaglate (1 product). All

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products are prescription-only medicines. As on 23 December 2015, the DH has not received any ADR case related to ICM products. In view of the above FDA announcement, the DH issued a letter to inform local healthcare professionals on 18 November 2015. The matter will be discussed by the Registration Committee of the Pharmacy and Poisons Board.

Drug Recall

Recall of eight pharmaceutical products manufactured by Europharm

On 6 November 2015, the DH endorsed a licensed drug manufacturer, Europharm Laboratoires Co Ltd (Europharm), to recall six products from the market because the names and quantities of excipients used in these products do not match with the registered particulars. The six products are Euro-Antinal Capsules 200mg (HK-41562), Naswall Capsules 200mg (HK-54739), Bovill Capsules 200mg (HK-54740), Melitte Capsules 200mg (HK-54741), Davicoff Capsules (HK-54742) and Sinpress Capsules 200mg (HK-54743).

Acting on a complaint, investigation has been carried out against Europharm and it was found that the company has added an additive, namely hydroxypropyl cellulose, into the formulation of the above six products. Hydroxypropyl cellulose is a common additive used in pharmaceutical products to facilitate binding of the ingredients. However, such changes in the formulation have not been approved by the Pharmacy and Poisons Board and render the products unregistered. Since the supply of unregistered pharmaceutical products contravenes the Pharmacy and Poisons Regulations (Cap 138A), Europharm has voluntarily recalled the products from the market.

The above-mentioned products, all containing Nifuroxazide, are over-the-counter medicines used for the treatment of diarrhoea.

On 11 November 2015, the DH endorsed Europharm again to recall respectively two batches of Maxicold Tablets ((HK-48879, batch numbers: B406178 and B412028) and Opticold Tablets (HK-48878, batch numbers: A406178 and A412028) from the market because the names and quantities of excipients used in these products do not match with the registered particulars.

Following the recall of six products by Europharm on 6 November, the DH's investigation further identified that the company has added two additives, namely hydroxypropyl cellulose and Croscarmellose sodium into the formulation of the above two products, without prior approval from the Pharmacy and Poisons Board. Hydroxypropyl cellulose and Croscarmellose sodium are common additives used in pharmaceutical products to facilitate binding of the ingredients and disintegration of the tablets respectively.

Investigation indicated that only the above-mentioned four batches of products were affected and considered as unregistered. Since the supply of unregistered pharmaceutical products contravenes the Pharmacy and Poisons Regulations (Cap 138A), Europharm voluntary recalls the products from the market.

The above-mentioned products, both containing paracetamol and brompheniramine, are over-the-counter medicines used for the treatment of common cold symptoms. According to Europharm, the affected eight products have been supplied to private doctors, local pharmacies and medicine companies. As on 23 December 2015, the DH has not received any adverse reports in connection with the concerned products. The DH will closely monitor the recalls. Notices were released on the website of the Drug Office on 6 November and 11 November 2015 to alert the public of the recalls.

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.

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

Fax: 3904 1224

E-mail: pharmgeneral@dh.gov.hk

Adverse Drug Reaction (ADR) Reporting:

Tel: 2319 2920

Fax: 2319 6319

E-mail: adr@dh.gov.hk

Link: http://www.drugoffice.gov.hk/adr.html

Post: ***Pharmacovigilance Unit,***
Drug Office, Department of Health,
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