Drug News
藥 物 情 報

Issue Number 100

This is a monthly digest of local and overseas drug safety news released by the Drug Office of the Department of Health in February 2018 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

UK: Misoprostol vaginal delivery system (Mysodelle): reports of excessive uterine contractions (tachysystole) unresponsive to tocolytic treatment

On 6 February 2018, the Medicines and Healthcare products Regulatory Agency (MHRA) of the United Kingdom (UK) announced that Mysodelle can cause uterine tachysystole that may not respond to tocolytic treatment.

A routine European Union (EU) review of Mysodelle investigated reports from a study in which 13% of women (90 of 678 patients) randomly assigned to the 200mcg misoprostol vaginal insert developed uterine tachysystole requiring intervention. In 5 cases (0.7% of women), uterine tachysystole did not subside with the use of tocolysis. Uterine tachysystole has been associated with poor uterine placental perfusion leading to a decrease in foetal oxygenation and eventually foetal compromise. In the study, despite the higher incidence of tachysystole requiring intervention recorded in women given the misoprostol vaginal insert than those given a dinoprostone vaginal insert (13% versus 4%, respectively), neonatal outcomes did not appear to differ.

The EU routine review of these cases concluded that uterine tachysystole that may not respond to tocolytic treatment can be caused by Mysodelle, even when used in accordance with the product information. The product information for Mysodelle in UK has been updated to reflect this finding, and with actions to take to ensure that this risk is adequately managed.

Healthcare professionals are advised to:

- Monitor patients closely and remove the vaginal delivery system immediately if any of the following apply:
  - tachysystole: more than 5 contractions in a 10-minute window, averaged over a 30-minute window;
  - prolonged contractions: single contractions lasting 2 minutes or longer;
  - hypertonic contractions: contractions that are too frequent and a high resting tone in the uterus.
- Also remove the vaginal delivery system in the following instances:
  - there is a clinical concern for the mother or baby;
  - onset of labour: rhythmic, firm contractions of adequate quality associated with cervical change, and/or at the latest when cervical dilation is 4 cm;
  - when 24 hours have elapsed since insertion.
- Be prepared to administer tocolytic therapy; should this be needed, it can be administered immediately after removal of Mysodelle.

In Hong Kong, Misodel Vaginal Delivery System 200mcg (HK-64060) is a vaginal delivery system containing misoprostol. It is a pharmaceutical product registered by Ferring Pharmaceuticals Ltd, and is a prescription-only medicine. As on 5 March 2018, the Department of Health (DH) has not received any case of adverse drug reaction (ADR) related to misoprostol. In light of the above MHRA's announcement, DH issued a letter to inform local healthcare professionals to draw their attention on 7 February 2018. The matter will be discussed by the Registration Committee of the Pharmacy and Poisons Board (the Registration Committee).

EU: Women taking Esmya for uterine fibroids to have regular liver tests while EMA review is ongoing. No new patients should start treatment for the time being.

On 9 February 2018, the European Medicines Agency (EMA) of EU announced that EMA's Pharmacovigilance Risk Assessment Committee (PRAC) is currently reviewing the benefits and risks with Esmya (ulipristal acetate), following reports of serious liver injury, including liver failure leading to transplantation.

As a temporary measure while the review is ongoing, PRAC has recommended regular liver monitoring for women taking Esmya for uterine fibroids. All women taking Esmya should have a liver function test at least once a month during treatment. If the test is abnormal (liver enzyme levels more than 2 times the upper limit of normal), the healthcare professional should stop treatment and closely monitor the patient. Liver tests should be repeated 2 to 4 weeks after stopping treatment.

PRAC is also recommending that no new patients should be started on Esmya and no patients who have completed a course of treatment should start another one for the time being.

A link between Esmya and cases of serious liver injury is under review. These recommendations are temporary measures to protect patients' health, pending the conclusion of the review of Esmya which started 30 November 2017.

In Hong Kong, Esmya Tablets 5mg (HK-62553) is a pharmaceutical product registered by Orient Europharma Co. Ltd, and is a prescription-only medicine. Related news was previously issued by EMA, and was reported in the Drug News Issue No. 98. As on 5 March 2018, DH has not received any case of ADR related to Esmya. In light of the above EMA's announcement, DH issued a letter to inform local healthcare professionals to draw their attention on 12 February 2018. As the review of Esmya is ongoing, DH remains vigilant on the conclusion of the review and safety update of the drug issued by other overseas drug regulatory authorities.

EU: PRAC recommends new measures to avoid valproate exposure in pregnancy. New restrictions on use; pregnancy prevention programme to be put in place.

On 9 February 2018, EMA announced that EMA's PRAC is recommending new measures to avoid exposure of babies to valproate medicines in the womb. Babies exposed are at risk of malformations and developmental problems.

Medicines containing valproate have been approved nationally in EU to treat epilepsy, bipolar disorder and in some countries for prevention of migraine. They are known to pose a considerable risk of malformations and developmental problems in babies who are exposed to valproate in the womb. An earlier review had recommended measures aimed at better informing women about these risks in order to reduce use of the medicine during pregnancy, and not starting treatment unless other options were ineffective or could not be used because of side effects. The current review was launched because of concerns that these measures had not been sufficiently effective.

PRAC examined the available evidence and consulted widely with healthcare professionals and with patients, including women and their children who have been affected by valproate use during pregnancy, through written submissions, expert meetings, meetings with stakeholders including healthcare professionals, patients organisations, patients and their families, and via a public hearing. PRAC noted that women were still not always receiving the right information in a timely manner and that further measures were needed to help avoid use during pregnancy. However, it was also clear that for some women, such as those with particular forms of epilepsy, valproate is the only appropriate treatment and might be life-saving.

PRAC therefore considered that the way the products are used should be changed. It recommended strengthening restrictions on their use and introducing new measures to require appropriate counselling and information for affected women.

PRAC also recommended that the companies

marketing these medicines carry out additional studies to further characterise the nature and extent of the risks posed by valproate and to monitor ongoing valproate use and the long-term effects from affected pregnancies.

The main measures recommended include:
- Where licensed for ***migraine*** or ***bipolar disorder***:
  - In *pregnancy* - valproate must not be used.
  - In *female patients from the time they become able to have children* - valproate must not be used unless the conditions of a new ***pregnancy prevention programme (PPP)*** are met.
- For ***epilepsy***:
  - In *pregnancy* - valproate must not be used. However it is recognised that for some women with epilepsy it may not be possible to stop valproate and they may have to continue treatment (with appropriate specialist care) in pregnancy.
  - In *female patients from the time they become able to have children* - valproate must not be used unless the conditions of the new ***PPP*** are met.
- PRAC has also recommended that the outer packaging of all valproate medicines must include a ***visual warning*** about the risks in pregnancy. In addition to boxed text, this may include a symbol/ pictogram, with the details to be adapted at national level.
- A ***patient reminder card*** will also be attached to the outer package for pharmacists to discuss with the patient each time the medicine is dispensed.
- Companies that market valproate should also provide ***updated educational materials*** in the form of guides for healthcare professionals and patients.

In Hong Kong, there are 12 registered pharmaceutical products containing valproic acid and/or valproate, and all products are prescription-only medicines. News related to recommendations to strengthen restrictions on the use of valproate medicines in women of childbearing age was previously issued by various overseas drug regulatory authorities, and was reported in the Drug News Issue No. 2, 21, 43, 60, 61 and 90. DH issued letters to inform local healthcare professionals to draw their attention on 7 May 2013 and 13 October 2014. In December 2014, the Registration Committee discussed the findings of an EMA's previous review on the risks of valproate products in pregnancy and had decided that warnings and precautions on the risks in pregnancy should be included in valproate products. As on 5 March 2018, DH has received 8 cases of ADR in connection with valproic acid or valproate, but none of them was related to adverse effects in new-born babies whose mothers took valproate for their medical conditions.

In light of the above EMA's announcement, DH issued a letter to inform local healthcare professionals to draw their attention on 12 February 2018. As the PRAC new recommendations will now be sent to Co-ordination Group for Mutual Recognition and Decentralised Procedures – Human (CMDh) for further adoption, DH remains vigilant on the development of the issue and safety update of the drug issued by other overseas drug regulatory authorities.

EU: PRAC recommends updating measures for pregnancy prevention during retinoid use. Warning on possible risk of neuropsychiatric disorders also to be included for all oral retinoids.

On 9 February 2018, EMA announced that EMA's PRAC has concluded its review of retinoid medicines and has recommended updating the measures for pregnancy prevention and including a warning on the possible risk of neuropsychiatric disorders (such as depression, anxiety and mood changes). Retinoids include the active substances acitretin, adapalene, alitretinoin, bexarotene, isotretinoin, tazarotene and tretinoin. They are taken by mouth or applied as creams or gels to treat several conditions mainly affecting the skin, including severe acne and psoriasis. Some retinoids are also used to treat certain forms of cancer.

During its review, PRAC assessed the available data including published literature and post-marketing reports of side effects, and also sought the views of patients and healthcare professionals in a dedicated stakeholder meeting and a successive written consultation. The PRAC recommendations are summarised below.

Regarding pregnancy prevention, PRAC confirmed that all oral (taken by mouth) retinoids can have

harmful effects on the unborn child and therefore must not be used during pregnancy. In addition, the oral retinoids acitretin, alitretinoin and isotretinoin must not be taken by women able to have children unless the conditions of a PPP are met. Although PPPs for these retinoids were already in place in some EU Member States, PRAC has now updated and harmonised the PPP to ensure it is optimal to support the discussion between the doctor and the patient on the risks of these medicines, and that it is followed in practice. In particular, the new PPP includes assessing patients for the likelihood of becoming pregnant, requirements around pregnancy testing and the need for effective contraception before, during and after treatment, and ensuring that patients and prescribers go through an 'acknowledgement form' to confirm that appropriate advice has been given. Educational materials for doctors and a reminder card for patients will also be provided.

The companies that market acitretin, alitretinoin and isotretinoin will also conduct a study and a survey to assess the effectiveness of the updated measures, particularly to check how the PPP is implemented.

For the oral retinoids bexarotene and tretinoin, a PPP was not considered necessary because these medicines, which are used to treat certain cancers, are used in a very different patient population under strict medical supervision and the current measures are considered appropriate for pregnancy prevention.

For topical (applied to the skin) retinoids, the data showed that the amount of active substance absorbed from the skin into the body is extremely low, and therefore these products are unlikely to cause harm to the unborn child. However, excessive use or skin lesions could possibly increase the absorption of retinoids. Therefore, as a precaution, PRAC recommended that topical retinoids must also not be used during pregnancy and in women planning to have a baby.

PRAC also reviewed the available data on the possible risk of neuropsychiatric disorders such as depression, anxiety and mood changes with retinoids. Although warnings about this possible risk were already included in the product information for some oral retinoids in EU, PRAC reviewed the extent and nature of these warnings to ensure that they reflect the available evidence, and that they are applied consistently.

For oral retinoids, PRAC noted the limitations of the available data, and considered that it could not be clearly established whether this risk was due to the use of these medicines. However, PRAC recognised that patients with severe skin conditions may be more vulnerable to neuropsychiatric disorders due to the nature of the disease. PRAC therefore recommended that the prescribing information for all oral retinoids should include a warning about this risk, including signs and symptoms patients and their families should be aware of (such as changes in mood or behaviour).

For topical retinoids, the available data, although extremely limited, suggest that these medicines do not carry a risk of psychiatric side effects and therefore no additional warnings need to be added to the prescribing information.

In Hong Kong, there are 49 registered pharmaceutical products containing retinoids, including acitretin (2 products), adapalene (14 products), isotretinoin (11 products), tazarotene (3 products) and tretinoin (19 products). All products are prescription-only medicines. There is no registered pharmaceutical product containing alitretinoin or bexarotene. Related news on initiation of review of retinoid medicines was previously issued by EMA. As on 5 March 2018, DH has received 2 cases of ADR related to isotretinoin associated with miscarriage and ectopic pregnancy. DH has also received 3 cases of ADR related to tretinoin, but none of them was related to adverse effects in pregnancy and of neuropsychiatric disorders. DH has not received any case of ADR related to other retinoids.

In light of the above EMA's announcement, DH issued a letter to inform local healthcare professionals to draw their attention on 12 February 2018. As the PRAC recommendations will now be sent to the Committee for Medicinal Products for Human Use for further adoption, DH remains vigilant on the development of the issue and safety update of the drugs issued by other overseas drug regulatory authorities.

Canada: TECENTRIQ (atezolizumab) - Risk of myocarditis

On 14 February 2018, Health Canada announced that severe cases of myocarditis have been reported in patients receiving TECENTRIQ treatment.

As of 20 February 2017, a cumulative analysis of the company's safety database, which includes data from clinical trials and the post-marketing setting, identified 2 non-fatal cases of myocarditis, including one case with biopsy confirmation. No Canadian cases of myocarditis related to TECENTRIQ treatment have been identified as of February 2017. Approximately 8,000 patients in clinical trials and 5,000 patients in the post-market setting have been exposed to TECENTRIQ as of November 2016. In some patients, TECENTRIQ has been associated with the risk of developing myocarditis. Myocarditis is an inflammation of the heart muscle, leading to possible reduction in the heart's pumping function and to possible irregular heartbeat.

Patients should contact their healthcare professional if they develop the following signs and symptoms during treatment with TECENTRIQ: chest pain; irregular heartbeat; shortness of breath at rest or during physical activity; fluid retention with swelling of legs, ankles and feet; decreased exercise tolerance.

Healthcare professionals are advised to:
- monitor patients receiving TECENTRIQ for signs and symptoms of myocarditis;
- withhold TECENTRIQ therapy in patients with Grade 2 myocarditis;
- permanently discontinue TECENTRIQ treatment in patients with Grade 3 or 4 myocarditis;
- administer corticosteroids and/or additional immunosuppressive agents as clinically indicated to TECENTRIQ treated patients who develop myocarditis.

The Canadian Product Monograph has been updated to include this new safety information.

In Hong Kong, Tecentriq Concentrate for Solution for Infusion 1200mg/20ml (HK-65567) is a pharmaceutical product registered by Roche Hong Kong Limited, and is a prescription-only medicine. As on 5 March 2018, DH has received 9 cases of ADR related to atezolizumab, but these cases were not related to myocarditis. In light of the above Health Canada's announcement, DH issued a letter to inform local healthcare professionals to draw their attention on 15 February 2018. The matter will be discussed by the Registration Committee.

US: Clarithromycin (Biaxin): Potential increased risk of heart problems or death in patients with heart disease

On 22 February 2018, the United States (US) Food and Drug Administration (FDA) is advising caution before prescribing the antibiotic clarithromycin (Biaxin) to patients with heart disease because of a potential increased risk of heart problems or death that can occur years later. FDA's recommendation is based on a review of the results of a 10-year follow-up study of patients with coronary heart disease from a large clinical trial that first observed this safety issue.

The large clinical trial, called the CLARICOR trial, observed an unexpected increase in deaths among patients with coronary heart disease who received a two-week course of clarithromycin that became apparent after patients had been followed for one year or longer. There is no clear explanation for how clarithromycin would lead to more deaths than placebo. Some observational studies also found an increase in deaths or other serious heart-related problems, while others did not. All the studies had limitations in how they were designed. Of the six observational studies published in patients with or without coronary artery disease, two found evidence of long-term risks from clarithromycin, and four did not. Overall, results from the prospective, placebo-controlled CLARICOR trial provide the strongest evidence of the increase in risk compared to the observational study results. Based on these studies, FDA is unable to determine why the risk of death is greater for patients with heart disease.

As a result, FDA added a new warning about this increased risk of death in patients with heart disease, and advised prescribers to consider using other antibiotics in such patients. FDA also added the study results to the clarithromycin drug labels. As part of FDA's usual ongoing safety monitoring

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of drugs, FDA is continuing to monitor safety reports in patients taking clarithromycin.

Healthcare professionals should be aware of these significant risks and weigh the benefits and risks of clarithromycin before prescribing it to any patient, particularly in patients with heart disease and even for short periods, and consider using other available antibiotics. Healthcare professionals should also advise patients with heart disease of the signs and symptoms of cardiovascular problems, regardless of the medical condition treating with clarithromycin.

In Hong Kong, there are 52 registered pharmaceutical products containing clarithromycin, and are prescription-only medicines. As on 5 March 2018, DH has received 8 cases of ADR related to clarithromycin, of which one case was related to cardiac arrest. In light of the above FDA's announcement, DH issued a letter to inform local healthcare professionals to draw their attention on 23 February 2018. The matter will be discussed by the Registration Committee.

Drug Recall

DH endorsed batch recall of Lynparza Capsules 50mg (HK-64538)

On 21 February 2018, DH endorsed a licensed drug wholesaler, AstraZeneca Hong Kong Limited (AstraZeneca), to recall 3 batches (Batch No.: NG699, NF848, NJ141) of Lynparza Capsules 50mg (HK-64538) from the market due to potential quality issue.

DH received notification from AstraZeneca that, during the ongoing stability testing of the above product, the manufacturer of the product in US found that samples of the above batches may have a potential trend to exceed the limit set of the crystalline form of the active ingredient. Based on the preliminary investigation of the manufacturer, the issue is related to certain batches of active ingredient raw materials. Although the product passed all testing in the ongoing stability study, AstraZeneca recalls the affected batches as precautionary measure.

The above product, containing olaparib, is a prescription medicine used for treatment of *BRCA*-mutated ovarian cancer.

According to AstraZeneca, 1,320 bottles containing 112 capsules per bottle of the affected batches have been supplied to the Hospital Authority (HA), private hospitals, private doctors and exported to Macao.

As on 5 March 2018, DH has not received any ADR case in connection with the affected batches of product. A notice was posted on the Drug Office website on 21 February 2018 to alert the public of the product recall.

Drug Incident

DH urged public not to buy or use two external products of doubtful composition

On 13 February 2018, DH appealed to the public not to buy or use two external products (English names are not available, Chinese names: 无癣膏 and 滇王银癣净) as they were found to contain undeclared controlled ingredients.

Acting upon intelligence, DH purchased samples of the above products from a retail premise in North Point for analysis. The test results from the Government Laboratory revealed that the samples contained two Part 1 poisons under the Pharmacy and Poisons Ordinance (Cap 138), namely clobetasol propionate and miconazole.

Clobetasol propionate is a steroid substance for treating inflammation and inappropriate or excessive application of steroids could cause skin problems and body-wide side effects like moon face, high blood pressure, high blood sugar, muscle atrophy, adrenal insufficiency and osteoporosis. Products containing clobetasol propionate should be used under a doctor's directions and be supplied

in a pharmacy under the supervision of a registered pharmacist upon a doctor's prescription. Miconazole is used for the treatment of fungal infection with side effects such as local irritation and sensitivity reactions.

A notice was posted on the website of Drug Office on 13 February 2018 to alert the public of the drug incident.

Public urged not to buy or consume slimming products with doubtful composition

On 14 February 2018, DH appealed to the public not to buy or consume four slimming products as they were found to contain undeclared ingredients. The products are:

(i) CA NI CAP Arm Slim (sibutramine found);
(ii) 7 Days Slim hip & Legs (sibutramine found);
(iii) Slim Perfect Legs (sibutramine found); and
(iv) CA NI Slim BELLANCE (orlistat found).

Following a public complaint, samples of the above products were purchased from an Internet seller for analysis. Test results from the Government Laboratory revealed that the samples either contain sibutramine or orlistat, which are Part 1 poisons under the Pharmacy and Poisons Ordinance (Cap 138).

Sibutramine was once used as an appetite suppressant. Since November 2010, products containing sibutramine have been banned in Hong Kong because of increased cardiovascular risk. Orlistat is used for the treatment of obesity. Its side-effects include faecal urgency, fatty stool, increased frequency of defecation, faecal incontinence, headache and abdominal pain. Severe liver injuries may also be induced.

Weight control should be achieved through a balanced diet and appropriate exercise. The public should consult healthcare professionals before using any medication for weight control.

The public may visit the Drug Office's pages for health messages on weight control and slimming products (http://www.drugoffice.gov.hk/eps/do/en/consumer/slim.html) and information on slimming products with undeclared Western drug ingredients (http://www.drugoffice.gov.hk/eps/specMedsNews/slimming/en/consumer).

A notice was posted on the website of Drug Office on 14 February 2018 to alert the public of the drug incident.

Public urged not to buy or consume slimming product from unknown sources or of doubtful composition

On 22 February 2018, DH appealed to the public not to buy or consume a slimming product named SIN DEN BEAUTY as it was found to contain undeclared and banned drug ingredients that might be dangerous to health.

DH commenced investigation upon receipt of notification from HA regarding a female patient with a history of consuming the above slimming product. The patient was admitted to hospital for acute psychosis. Sibutramine metabolites were detected in her urine sample.

According to testing results from HA, which were later confirmed by the Government Laboratory, the sample of the product provided by the patient was found to contain the banned substances sibutramine and phenolphthalein.

Preliminary investigation revealed that the patient purchased the slimming product through a social media network platform.

Sibutramine was once used as an appetite suppressant. Since November 2010, products containing sibutramine have been banned in Hong Kong because of increased cardiovascular risk. Phenolphthalein was once used to treat constipation, but has been banned in Hong Kong for its cancer-causing effect.

Weight control should be achieved through a balanced diet and appropriate exercise. The public should consult healthcare professionals before using any medication for weight control.

The public may visit the website of the Drug Office of DH for health messages on overweight problem and slimming products (http://www.drugoffice.gov.hk/eps/do/en/consumer/

slim.html) and information on slimming products with undeclared Western drug ingredients (http://www.drugoffice.gov.hk/eps/specMedsNews/slimming/en/consumer).

A notice was posted on the website of Drug Office on 22 February 2018 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 $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.

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
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,
Rm 1856, 18/F, Wu Chung House,
213 Queen's Road East,
Wan Chai, Hong Kong

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.