



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

Canada: New contraindications for Nuvaring (etonogestrel / ethinyl estradiol slow release vaginal ring)

It was noted from the website of Health Canada on 1 August 2014 that Merck Canada Inc., in consultation with Health Canada, informed the healthcare professionals of new contraindications that have been added to the Nuvaring Product Monograph (PM). Nuvaring is a combined hormonal contraceptive (CHC) indicated for conception control. The following points summarize the important changes that have been made to the PM:

- Nuvaring should NOT be used by women who smoke (if over age 35), or who have severe or multiple risk factors for thrombosis, including: valvular heart disease with complications, hypertension, severe dyslipoproteinemia, abnormality in proteins that regulate coagulation, diabetes mellitus with vascular involvement, or major surgery with prolonged immobilization.
- Nuvaring should NOT be used by women who have experienced migraines with focal neurological symptoms, or pancreatitis associated with severe hypertriglyceridemia.
- Prescribers should consider the above new contraindications and review the updated PM when discussing treatment options with their patients.

In addition to the above contraindications, changes have also been made under WARNINGS AND PRECAUTIONS section of the PM regarding the following possible adverse events: systemic lupus erythematosus, sydenham's chorea, herpes gestationis, otosclerosis-related hearing loss, hepatocellular carcinoma, Crohn's disease, colitis

ulcerosa and angioedema. Merck Canada Inc., in working with Health Canada, has updated the Nuvaring PM regarding the above new contraindications and warnings which are also associated with other CHC products.

In Hong Kong, Nuvaring Vaginal Rings (HK-55149) is a registered pharmaceutical product. It is registered by Merck Sharp & Dohme (Asia) Ltd. (MSD) and is a prescription only medicine. MSD has submitted application to update the package insert of its product with new safety information similar to the Health Canada's announcement. So far, the Department of Health (DH) has not received any local adverse drug reaction (ADR) report related to the product. In view of the Health Canada's announcement, a letter to healthcare professionals to draw their attention and urge them to report any ADRs related to the drug was issued on 1 August 2014. 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. The DH will remain vigilant on safety updates and regulatory actions related to the drug decided by other overseas health authorities.

The Mainland: Alert on trimetazidine and the association of risk of movement disorders

On 4 August 2014, the China Food and Drug Administration (CFDA) of the Mainland alerted on the risk of movement disorders associated with trimetazidine. Trimetazidine is a cardiovascular drug indicated for angina pectoris, and is also used in the symptomatic treatment of vertigo and

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tinnitus. Recently, the European Medicines Agency (EMA) announced that the proposal to limit the use of trimetazidine for patients with angina pectoris, and keep vigilant on the risk of movement disorders.

Based on the data from the National Centre for ADR Monitoring of the Mainland, and the results of analysis from the EMA, the CFDA recommends:

- Trimetazidine is indicated for patients with stable angina pectoris who are inadequately controlled by or intolerant to first-line antianginal therapies. It should no longer be used for tinnitus and vertigo treatment.

- By prohibiting the use of trimetazidine on patients with Parkinson's disease, Parkinson's syndrome, tremor, restless legs syndrome, and other related movement disorders and severe renal impairment (creatinine clearance < 30ml/min).

- Should pay close attention when the use of trimetazidine is given which may cause adverse reactions such as: Parkinsonism (tremor, akinesia, and hypertonia), ataxia, restless leg syndrome, movement disorders and other related agranulocytosis, thrombocytopenia, thrombocytopenic purpura and hepatitis.

- The dose should be appropriately adjusted for the moderate renal impairment (creatinine clearance 30-60ml/min) patients and elderly patients.

- Drug-related risk manufacturers should promptly inform the medical staff and patients, to strengthen the monitoring of adverse drug reactions, and to take effective measures to maximize the protection of the patient's medication safety.

In Hong Kong, there are eight registered pharmaceutical products containing trimetazidine and they are prescription only medicines. Related news had been released by EMA and was reported in Drug News Issue No. 32. A letter to healthcare professionals to draw their attention and urge them to report any ADRs related to the drug was issued, and the matter had already been discussed in the meeting of the Registration Committee in May 2014. The Committee decided that the sales pack labels and/or package inserts of products containing trimetazidine should include the following new safety information:

Indication

- *Trimetazidine is indicated in adults as add-on therapy for the symptomatic treatment of patients with stable angina pectoris who are inadequately controlled by or intolerant to first-line antianginal therapies.*

- *For the symptomatic treatment of tinnitus, vertigo and visual field disturbances, the European Union (EU) health authority concluded that the benefits no longer outweigh the risks and that these uses should no longer be authorised.*

Contraindications

- *Hypersensitivity to the active substance or to any excipients of the products.*

- *Parkinson disease, parkinsonian symptoms, tremors, restless leg syndrome, and other related movement disorders.*

- *Severe renal impairment (creatinine clearance <30ml/min).*

Special warnings and precautions for use

- *Trimetazidine can cause or worsen parkinsonian symptoms (tremor, akinesia, hypertonia), which should be regularly investigated, especially in elderly patients. In doubtful cases, patients should be referred to a neurologist for appropriate investigations.*

- *The occurrence of movement disorders such as parkinsonian symptoms, restless leg syndrome, tremors, gait instability should lead to definitive withdrawal of trimetazidine.*

- *These cases have a low incidence and are usually reversible after treatment discontinuation. The majority of the patients recovered within 4 months after trimetazidine withdrawal. If parkinsonian symptoms persist more than 4 months after drug discontinuation, a neurologist opinion should be sought.*

- *Falls may occur, related to gait instability or hypotension, in particular in patients taking antihypertensive treatment.*

- *Caution should be excised when prescribing trimetazidine to patients in whom an increased exposure its expected :*

- (a) *moderate renal impairment*

- (b) *elderly patients older than 75 years old*

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Singapore: New warning on serious skin reactions (Stevens Johnson syndrome and acute generalised exanthematous pustulosis) with Reminyl® (galantamine hydrobromide)

It was noted from the website of Health Sciences Authority (HSA) on 7 August 2014 that Janssen, a division of Johnson & Johnson Pte Ltd, alerted healthcare professionals to the risk of serious skin reactions that have been reported with the use of Reminyl® (galantamine hydrobromide). Stevens Johnson syndrome (SJS) and acute generalised exanthematous pustulosis (AGEP) have been reported in patients receiving Reminyl®. Patients should be informed about the signs of serious skin reactions, and that use of Reminyl® should be discontinued at the first appearance of skin rash. These warnings regarding serious skin reactions are in the process of being updated in the Reminyl® Singapore package insert, with SJS and AGEP to be included as new adverse reactions.

In Hong Kong, there are five registered pharmaceutical products containing galantamine hydrobromide, namely Reminyl Oral Solution 4mg/ml (HK-49407), Reminyl Prolonged Release Cap 24mg (HK-55292), Reminyl Prolonged Release Cap 8mg (HK-55293), Reminyl Prolonged Release Cap 16mg (HK-55294), HC Galanthamine Hydrobromide Dispersible Tablets 4mg (HK-62303). All of the products are prescription only medicines, and are indicated for the treatment of mild to moderately severe dementia of the Alzheimer type. So far, the DH has not received any local ADR report of serious skin reactions related to the drug. In view of the HSA's announcement, a letter to healthcare professionals to draw their attention and urge them to report any ADRs related to the drug was issued on 7 August 2014, and the matter will be discussed in the meeting of the Registration Committee. The DH will remain vigilant on safety updates and regulatory actions related to the drug decided by other overseas health authorities.

EU: CMDh endorses restricted use of bromocriptine for stopping breast milk production

On 21 August 2014, the Coordination Group for Mutual Recognition and Decentralised Procedures – Human (CMDh) has endorsed by majority recommendations on the use of bromocriptine-

containing medicines by mouth to prevent or suppress breast milk production (lactation) after childbirth. The CMDh agreed that the medicines should only be used for this purpose (in strengths up to 2.5 mg) when there are compelling medical reasons.

The CMDh position follows a review by the EMA's Pharmacovigilance Risk Assessment Committee (PRAC) of available data on the safety and effectiveness of bromocriptine in controlling breast milk production after childbirth, which led to these recommendations. The review was triggered by concerns in France over increased reports of rare but potentially serious or fatal side effects, particularly cardiovascular side effects, neurological side effects such as seizures and psychiatric side effects. Since lactation is a natural process that eventually stops if the infant is not breastfed, and other means of management are available, the French medicines agency (ANSM) asked the EMA to review the medicines and see if the benefits of such use still outweighed the risks. As the CMDh position on bromocriptine was adopted by majority vote, it will now be sent to the European Commission, which will take an EU-wide legally binding decision.

Healthcare professionals are advised that the following recommendations (some of which are already included in the product information) should be borne in mind when prescribing bromocriptine for the prevention or suppression of lactation.

- Bromocriptine should only be used orally in strengths up to 2.5 mg to inhibit lactation when medically indicated, such as in case of intrapartum loss, neonatal death or HIV infection of the mother. Products with strengths of 5 or 10 mg are not indicated for such use.
- Bromocriptine should not be used for the routine suppression of lactation, nor for the relief of symptoms of post-partum pain and engorgement, which can be adequately treated with non-pharmacological intervention (such as firm breast support, ice application) and simple analgesics.
- Use is contraindicated for patients with uncontrolled hypertension, hypertensive disorders of pregnancy, hypertension post-partum and in the puerperium, a history of coronary artery disease or other severe cardiovascular conditions, or a history of severe psychiatric disorders.

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- Blood pressure should be carefully monitored especially during the first day of therapy. If hypertension, suggestive chest pain, severe, progressive, or unremitting headache or evidence of central nervous system toxicity develops, treatment should be discontinued and the patient evaluated promptly.

In Hong Kong, there are seven registered pharmaceutical products containing bromocriptine which are prescription only medicines. Related news has been released by the EMA, and was posted in the Drug News Issue No. 57. A letter to healthcare professionals draw their attention and urge them to report any ADR related to the drug was issued on 14 July 2014. So far, the DH has not received any local adverse drug reaction report related to the drug. In view of the EMA's announcement, the matter will be discussed in the meeting of the Registration Committee. The DH will remain vigilant on any safety updates of the drugs and regulatory actions taken by other overseas health authorities.

Canada: Safety review regarding the possible risk of thrombotic microangiopathy with the use of interferon-beta products

On 22 August 2014, Health Canada announced a safety review was initiated to evaluate the currently available information regarding the possible risk of thrombotic microangiopathy (TMA), a blood clotting disorder affecting small blood vessels, with the use of interferon-beta products.

To assess the available evidence concerning the risk of developing TMA following exposure to any interferon-beta product. This review considered Canadian adverse reaction reports, scientific and medical literature, and international safety data, as well as what is known about the use of these products both in Canada and internationally, and evaluated the possible risk of TMA.

A small number of cases of TMA after exposure to interferon-beta products have been reported in Canada and internationally. The scientific literature does not clearly explain why interferon-beta products can cause TMA.

Given the limited information available at the time of this review, Health Canada decided to continue its ongoing monitoring of adverse reaction information involving interferon-beta products, as it does for all health products, to identify and assess potential harms. Health Canada will keep Canadians informed and take action, as appropriate, if any new safety information is identified.

In Hong Kong, there are 11 registered pharmaceutical products containing interferon-beta which are prescription only medicines. Interferon beta is mainly used in the management of relapsing-remitting multiple sclerosis. In view of the Health Canada's announcement, a letter to healthcare professionals to draw their attention and urge them to report any ADRs related to the drug was issued on 25 August 2014. The DH remains vigilant on any safety updates related to the drug and actions taken by other overseas regulatory authorities.

Drug Recall

Batch recall of Viartril-S Solution for Injection (Biologici) (HK-60732)

On 1 August 2014, the DH endorsed a licensed drug wholesaler, LF Asia (HK) Ltd - Healthcare Division (LF Asia), to conduct a voluntary recall of one batch (batch number: E12001) of Viartril-S Solution for Injection (Biologici) [Viartril-S] from the market due to a potential non-compliance in the Good Manufacture Practice (GMP) of the manufacturer of lignocaine hydrochloride which is one of the ingredients of the product. Viartril-S containing glucosamine sulphate and lignocaine hydrochloride is indicated for osteoarthritis. It can

only be sold in pharmacy under the supervision of registered pharmacist.

DH received notification from LF Asia that the Italian manufacturer of lignocaine hydrochloride was found not in compliance with the GMP requirements during an inspection by the Italian Medicine Agency. According to information provided by the product manufacturer, although the batch of lignocaine hydrochloride (batch number: 162917) used for manufacturing of the batch (batch number: E12001) of Viartril-S imported into Hong Kong was not affected, a recall is initiated as a precautionary measure.

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According to LF Asia, 1500 boxes of the affected batch were imported to Hong Kong in November 2012. Among the imported stock, about 570 boxes have been supplied to private doctors and pharmacies. Another 413 boxes were exported to Macao. The DH will closely monitor the recall. As on 1 August 2014, the DH had not received any adverse reaction report related to the use of the product. A notice was released on the Drug Office's website on the same day to alert the public of the recall.

Recall of Spersallerg Eye Drops (HK-29793)

On 8 August 2014, the DH endorsed a licensed drug wholesaler, Novartis Pharmaceuticals (HK) Ltd (Novartis), to recall all batches of Spersallerg Eye Drops from the market due to potential quality issue. Spersallerg Eye Drops, containing antazoline and tetrahydrozoline, is an over-the-counter medicine for the treatment of allergic conjunctivitis.

The DH received notification from Novartis that the product's manufacturer in Switzerland was recalling all batches of Spersallerg Eye Drops globally from the market. According to Novartis, the manufacturer of one of the product's active ingredients was found to have violated the GMP requirements. Such violation may pose potential risk of cross-contamination of the raw material; and hence the recall is conducted as a precautionary measure.

According to the distributor, the product has been supplied to the Hospital Authority (HA), DH clinics, private hospitals, medical practitioners, pharmacies and medicine stores. The product has also been exported to Macao. The DH will closely monitor the recall. As on 8 August 2014, the DH had not received any adverse reaction report related to the use of the product. A press release was issued on the same day to alert the public of the recall.

Members of the public should stop using the product and seek advice from healthcare professionals if in doubt or feeling unwell after use.

Batch recall of Rivotril Oral Drops 2.5mg/ml (HK-03373)

On 18 August 2014, the DH endorsed a licensed drug wholesaler, Roche HK Ltd (Roche), to

conduct a voluntary recall of one batch (batch number: M1611M1) of Rivotril Oral Drops 2.5mg/ml [Rivotril] from the market due to incorrect package insert used in this batch of product. Rivotril containing clonazepam is indicated for epilepsy. It should only be used under medical advice. It can also be sold on prescription and under the supervision of registered pharmacist in pharmacy.

The DH received notification from Roche that the wrong package insert with incorrect storage condition was packed in one batch (batch number: M1611M1) of Rivotril. The correct storage condition should be "Do not store above 25°C" instead of the wrong version "Do not store above 30°C". According to Roche, the printing error only affected the package insert while the storage condition on the outer carton is the correct one. Inappropriate storage condition may affect the efficacy of the product.

According to Roche, 420 boxes of the affected batch were imported to Hong Kong in May 2014 and were then re-packed by its distributor. Among the imported stock, 407 boxes have been supplied to HA, private hospitals, private doctors and one pharmacy. The DH will closely monitor the recall. As on 18 August 2014, the DH had not received any adverse reaction report related to the use of the product. A notice was released on the Drug Office's website on the same day to alert the public of the recall.

Recall of Allerex Eye Drops (HK-54384) and Optodexine Eye Drops (HK-54304)

On 27 August 2014, the DH endorsed a licensed drug wholesaler, Ashford Pharmaceuticals Ltd., to recall from the market all batches of Allerex Eye Drops and Optodexine Eye Drops due to a potential quality issue. Allerex Eye Drops, containing antazoline and tetrahydrozoline, is an over-the-counter medicine for the treatment of allergic conjunctivitis. Optodexine Eye Drops, containing chloramphenicol, dexamethasone and tetrahydrozoline, is a prescription medicine for the treatment of eye infection

The DH received notification from the manufacturer of both pharmaceutical products in Macau that it is recalling Allerex and Optodexine Eye Drops from

Drug Recall

the market globally. According to the Macau manufacturer, the manufacturer of one of the products' active ingredients was found to have violated the GMP requirements. Such a violation may pose potential risks of cross-contamination of raw materials, and hence the recall is being conducted as a precautionary measure.

According to the distributor, both Allerex and Optodexine Eye Drops have been supplied to local private hospitals, medical practitioners and pharmacies while Allerex Eye Drops have also been supplied to the DH's clinics. The DH will closely monitor the recall. As on 27 August 2014, the DH had not received any adverse reaction report related to the use of the products. A notice was released on the Drug Office's website on the same day to alert the public of the recall.

Members of the public should stop using the products and seek advice from healthcare professionals if in doubt or feeling unwell after use.

Recall 4 batches of Serophene 50mg Tablet (HK-33272)

On 29 August 2014, the DH endorsed a licensed drug wholesaler, Merck Pharmaceutical (HK) Ltd. (Merck), to conduct a voluntary recall of four batches (S54009, S54013, S54015 and S54017) of

Serophene tablets 50mg from the market due to potential quality issue. Serophene tablet 50mg, containing clomiphene citrate, is a prescription medicine used for the treatment of infertility due to ovulation difficulty.

The DH received notification from Merck that the Israel manufacturer of the product had found the above 4 batches of the product were manufactured with raw material found to contain impurity. Although there is no evidence that the impurity in question would have adverse effects on health, Merck has decided to recall the affected batches from the market as a precautionary measure.

According to Merck, the affected batches were imported into Hong Kong between January 2012 and May 2013, and they had been supplied to private hospitals, private doctors and pharmacies. The DH will closely monitor the recall. As on 29 August 2014, the DH had not received any adverse reaction report related to the use of the product. A notice was released on the Drug Office's website on the same day to alert the public of the recall.

Healthcare providers should stop supplying the affected product to their clients. Members of the public who are consuming the product should consult their healthcare professionals if in doubt.

Drug Incident

Man arrested for suspected illegal sale of nicotine-containing liquid for electronic cigarettes

On 21 August 2014, a joint operation was conducted by the DH and the Police resulting in the arrest of a 30-year-old man for the suspected illegal sale of a nicotine-containing liquid. The liquid product is called "FEELVAPE" and is intended for use with electronic nicotine delivery systems, commonly known as electronic cigarettes.

Acting upon a public complaint, the DH found that the above product, labelled to contain nicotine (a Part I poison), was offered for sale on the Internet. During the operation, the seller was arrested by the Police for the suspected illegal sale of a Part I

poison and unregistered pharmaceutical product.

Under the Pharmacy and Poisons Ordinance (Cap 138), nicotine-containing electronic cigarette products are classified as pharmaceutical products requiring registration from the Pharmacy and Poisons Board of Hong Kong before they could be sold in Hong Kong.

Smokers who would like to quit smoking are welcome to call DH's Integrated Smoking Cessation Hotline 1833 183. Information on smoking cessation can also be obtained at the DH's Tobacco Control Office website (www.tco.gov.hk).

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.

Advice to Healthcare Professionals

Importance of infection control measures in preventing Ebola Virus Disease

On 7 August 2014, the DH issued a letter to all pharmacists to draw their attention to the recent reports of Ebola Virus Disease (EVD) in the Western Africa region, including Guinea, Liberia and Sierra Leone.

The outbreak was first reported in the Western African region to the World Health Organization (WHO) in March 2014. Latest distribution of cases can be found at the Centre for Health Protection (CHP) website: http://chp.gov.hk/files/pdf/evd_affected_area.pdf.

EVD, formerly known as Ebola haemorrhagic fever, is caused by Ebola virus. The disease is transmitted to human through contact with blood, secretions, organs or other body fluids of infected animals including chimpanzees, gorillas, fruit bats, monkeys, forest antelopes and porcupines. Human-to-human transmission is also possible through direct contact with blood, secretions, organs or other body fluids of infected people, and indirect contact with environments contaminated with such fluids. Healthcare workers have frequently been infected through close contact with patients when infection control measures are not strictly practiced.

The incubation period of the disease is around 2 to 21 days. Patients may present with sudden onset of fever, intense weakness, muscle pain, headache, sore throat, vomiting, diarrhoea, rash, followed by impaired kidney and liver function. In some severe cases, internal and external bleeding may occur.

No vaccine and specific treatment is available. The disease has a case fatality rate of up to 90%. People are infectious as long as their blood and secretions contain the virus. Men who have recovered from the disease can still transmit the virus through their semen for up to 7 weeks after recovery from illness.

In view of the risk of imported infections, healthcare professionals are reminded to strictly practise appropriate infection control measures in healthcare settings when managing suspected cases and keep abreast of latest development of the disease for providing suitable advices to patients or clients. The WHO has indicated that inadequate infection control measures will increase the risk of transmitting the disease to healthcare workers. Infection Control Branch of CHP has prepared the "Interim Recommendations on Infection Control for EVD in Healthcare Setting", available online at the following website: http://www.chp.gov.hk/files/pdf/ic_recommendations_for_evd.pdf.

The website provides recommendations on isolation of patients, use of protective equipment, and other infection control measures when managing the cases.

At the same time, the DH has strengthened relevant preventive measures in the community and at various ports. Outbound travellers are advised to avoid unnecessary travel to the affected area.

For further information on EVD, please visit the CHP website at http://www.chp.gov.hk/en/view_content/34199.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: 2186 9845

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.