



**D r u g**  
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**N e w s**  
**情 報**

## Issue Number 53

*This is a monthly digest of local and overseas drug safety news released by the Drug Office of the Department of Health in March 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: New contraindication on the use of high dose diclofenac for more than four weeks in selected groups of patients**

It was noted from the Health Sciences Authority (HSA) website on 1 March 2014 that the use of high dose systemic diclofenac (150mg/day) for more than four weeks is contraindicated in patients with established cardiovascular (CV) disease or uncontrolled hypertension. This regulatory decision was made following HSA's benefit-risk assessment, in consultation with its Product Vigilance Advisory Committee (PVAC) and several other clinical experts. The safety review was conducted in response to a growing body of scientific evidence suggesting that high doses of diclofenac used over a long duration is associated with increased CV risks. In addition to the new contraindication, healthcare professionals are advised that if diclofenac treatment is needed, patients with established CV disease, uncontrolled hypertension or significant CV risk factors (e.g. hypertension, hyperlipidaemia, diabetes mellitus and smoking) should be treated only after careful consideration and at doses  $\leq 100$  mg daily if the treatment is for more than 4 weeks. As the CV risks of diclofenac may increase with dose and duration of exposure, diclofenac should always be prescribed at the lowest effective daily dose and for the shortest duration possible.

In Hong Kong, there are 162 registered pharmaceutical products containing diclofenac indicated for systemic use (given by means such as capsules, tablets or injections) and are prescription only medicines. Safety alerts regarding diclofenac and other NSAIDs associated with cardiovascular risks had been released by MHRA and EMA and

were reported in Drug News Issues No. 24, 36 and 43. Letter to inform healthcare professionals was issued on 30 September 2011. As mentioned in Drug News Issue No. 43, the matter was discussed by the Registration Committee of the Pharmacy Poisons Board (the Registration Committee) in the meeting in February 2013 and the Registration Committee concluded that NSAIDs-containing products other than external preparations should include safety warnings regarding the cardiovascular risk. In view of HSA's latest recommendation, a letter to healthcare professionals was issued on 3 March 2014 and the matter will be further discussed in the meeting of the Registration Committee.

### **UK / US: Doribax (doripenem) - Recall in the UK and FDA approved label changes for describing increased risk of death for ventilator patients with pneumonia**

On 3 March 2014, the Medicines and Healthcare products Regulatory Agency (MHRA) of the United Kingdom (UK) announced that Janssen-Cilag Ltd. was recalling all batches within shelf life of Doribax (doripenem) 500mg powder for solution for infusion from all markets world-wide. The decision to recall was based on Janssen's continued portfolio review and followed from the decision to return the licence to Shionogi & Co. Ltd. There were no known quality or safety issues with the stock being recalled. The advice to physicians who are currently treating patients with Doribax is to allow patients to complete their course of treatment, whereas pharmacy can retain stock for that purpose and return stock once there are no patients currently on this therapy.

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Subsequent to the notice dated 5 January 2012 regarding the Food Drug Administration (FDA) statement on a recently terminated clinical trial with Doribax, FDA had concluded on 6 March 2014 that Doribax, which has been used to treat patients who develop pneumonia while on ventilators, carries an increased risk of death and lower clinical cure rates compared to use of imipenem and cilastatin for injection. Based on FDA's analysis of data from a three-year clinical trial that was prematurely stopped in 2011 due to these safety concerns, FDA had approved changes to the Doribax drug label that describe these risks. Doribax is not approved to treat any type of pneumonia in the US, and the revised label also includes a new warning about this unapproved use. Healthcare professionals are advised to consider whether the benefits of Doribax treatment are likely to exceed its potential risks in patients who develop pneumonia while on ventilators. Doribax is still considered safe and effective for its FDA-approved indications - treatment of adults with complicated intra-abdominal infections and complicated urinary tract infections, including kidney infections called pyelonephritis.

In Hong Kong, Doribax for Inj 500mg (HK57638) is registered by Johnson & Johnson (HK) Ltd. (J&J) and it is a prescription only medicine. According to the registered package insert, ventilator-associated pneumonia is one of the approved indications. This indication is also being approved in other drug regulatory authorities such as European Medicines Agency (EMA) and MHRA. Nevertheless, J&J had already issued a "Dear Healthcare Professional Communication" on 24 February 2014 to inform healthcare professionals about the discontinuation of the product and remark another treatment alternative for consideration. The arrangement for return and refund of the product was also notified. The Department of Health (DH) will keep vigilant against any updates of the drug.

## **EU: PRAC recommends restricting use of domperidone**

On 7 March 2014, European Medicines Agency (EMA) announced that the Pharmacovigilance Risk Assessment Committee (PRAC) had completed a review of domperidone-containing medicines,

which was carried out at the request of the Belgian medicines authority over concerns about the medicine's effects on the heart. And PRAC recommended that domperidone-containing medicines should remain available and may continue to be used in the EU for the management of the symptoms of nausea and vomiting. However, the recommended dose should be reduced to 10 mg up to three times daily by mouth for adults and adolescents weighing 35 kg or more. These patients may also be given the medicine as suppositories of 30 mg twice daily. Where the medicine is licensed in children and adolescents weighing less than 35 kg, it should be given by mouth at a dose of 0.25 mg per kg bodyweight up to three times daily. The medicine should not normally be used for longer than one week.

Besides, domperidone should no longer be authorised to treat other conditions such as bloating or heartburn. It must not be given to patients with moderate or severe impairment of liver function, or in those who have existing abnormalities of electrical activity in the heart or heart rhythm, or who are at increased risk of such effects. In addition, it must not be used with other medicines that have similar effects on the heart or reduce the breakdown of domperidone in the body (thus increasing the risk of side effects). Products supplying a dose of 20 mg by mouth, and suppositories of 10 or 60 mg are no longer recommended for use and should be withdrawn.

In Hong Kong, there are 51 registered pharmaceutical products containing the anti-emetic drug domperidone. News regarding the risk of cardiac disorder had been released by Health Canada and HSA and was reported in Drug News Issue No. 29. The issue had been discussed in the meeting of The Registration Committee on 28 February 2012. The Committee decided that the sales pack or package insert of domperidone-containing products should be updated to include safety information regarding the risk of cardiac disorder. In view of EMA's latest recommendations, a letter to inform healthcare professionals was issued on 10 March 2014, and the matter will be further discussed in the meeting of Registration Committee.

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### **EU: PRAC recommended product information of zolpidem be updated with new advice to minimise the risk of next-morning impaired driving ability and mental alertness**

On 7 March 2014, EMA announced that PRAC had completed a review of zolpidem-containing medicines and the benefit-risk balance of these medicines remains positive. However, PRAC had recommended changes to the product information of zolpidem, which aimed at minimising the known risks of next-morning impaired driving ability and mental alertness. PRAC considered that the recommended daily dose should remain at 10mg of zolpidem, and this dose must not be exceeded. Patients should take the lowest effective dose, in a single intake just before going to bed, and the medicine should not be taken again during the same night. In elderly patients and in patients with reduced liver function, the recommended dose remains 5 mg of zolpidem per day. Furthermore it is recommended not to drive or perform activities that require mental alertness until 8 hours after taking zolpidem. Zolpidem should not be taken together with other medicines that have an effect on the central nervous system (brain and spinal cord). Similarly, alcohol or other substances that affect mental function should not be used when taking zolpidem.

In Hong Kong, there are 16 registered pharmaceutical products containing zolpidem which include immediate-release 5mg or 10mg tablets and modified-release 6.25mg or 12.5mg tablets. All of them are prescription only medicines indicated for the treatment of insomnia. Zolpidem is also controlled as psychotropic substance internationally including Hong Kong. A letter to healthcare professionals was issued on 11 January 2013 and the concern was reported in Drug News Issue No. 39 and 43. The matter was discussed in the meeting of the Registration Committee in February 2013 and was concluded that the Drug Office should remain vigilant on any new safety update of zolpidem by other regulatory authorities for future consideration by the Registration Committee when necessary. In view of EMA's latest recommendations, the matter will be further discussed in the meeting of Registration Committee.

### **EU: Recommendations to restrict the use of diacerein-containing medicines**

On 7 March 2014, EMA announced that PRAC had re-examined diacerein-containing medicines and was recommending that they remain available but with restrictions to manage the risks of severe diarrhoea and effects on the liver. Due to the risks associated with severe diarrhoea, diacerein is no longer recommended in patients aged 65 years and above. It is also advised that patients start treatment on half the normal dose (i.e. 50mg daily instead of 100mg) and should stop taking diacerein if diarrhoea occurs. In addition, diacerein-containing medicines must now not be used in any patient with liver disease or a history of liver disease, and doctors are advised to monitor their patients for early signs of liver problems. PRAC further recommended that diacerein should only be started by doctors experienced in treating osteoarthritis and based on available data, the use of diacerein is to be limited to treating symptoms of osteoarthritis affecting the hip or knee.

On 21 March 2014, the Co-ordination Group for Mutual Recognition and Decentralised Procedures – Human (CMDh) endorsed the PRAC's final recommendations to address these concerns and ensure that the benefits of diacerein continue to outweigh its known risks.

In Hong Kong, there is one registered pharmaceutical product containing diacerein, namely Artrodar Cap 50mg (HK-56190). It is registered by TRB Chemedica HK Ltd. (TRB Chemedica) and is a prescription only medicine indicated for improving the pain and function in patients with osteoarthritis. Suspension of diacerein-containing medicines had been recommended by EMA and was reported in Drug News Issue No. 49. A letter to inform healthcare professionals was issued on 9 November 2013. The matter was discussed in the meeting of the Registration Committee in December 2013. The Registration Committee considered that TRB Chemedica would request EMA for re-examination of the recommendation and decided that DH should remain vigilant on any safety updates of diacerein by other health authorities and also the outcomes of the re-examination by EMA. In view of EMA's new recommendation to remain the drug available but with restrictions, a letter to inform healthcare

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professionals was issued on 24 March 2014, and the matter will be further discussed in the meeting of Registration Committee.

### **Australia: Natalizumab and melanoma**

On 18 March 2014, the Therapeutic Goods Administration (TGA) announced the concern of melanoma associated with natalizumab. Three cases of melanoma in patients being treated with natalizumab had been reported to the TGA. An ongoing TGA review of this issue had found insufficient evidence to show a definite link between natalizumab and melanoma. However, given the high incidence of melanoma in Australia, this remains an issue of concern for TGA. TGA is monitoring reports of melanoma in patients being treated with natalizumab and encouraging health professionals to report all such cases. TGA also advised health professionals who have prescribed natalizumab or are managing a patient who is taking this medicine are advised to monitor them for any new or changed skin lesions and ensure patients with any suspicious lesions undergo further investigation.

In Hong Kong, there is one registered pharmaceutical product containing natalizumab, namely Tysabri Concentrate for Solution for Infusion 300mg (HK-61519). It is a prescription only medicine indicated for the treatment of multiple sclerosis. DH had not received any adverse reaction report (ADR) in connection with the drug so far. In view of TGA's announcement, a letter to inform healthcare professionals to draw their attention and urge them to report any ADR related to the drug was issued on 18 March 2014. DH will keep vigilance on any safety updates of the drug and actions taken by other overseas regulatory authorities for consideration of any action deemed necessary.

### **Canada: Emergency contraceptive pills to carry warnings for reduced effectiveness in women over a certain body weight**

On 26 March 2014, Health Canada announced new warnings about reduced effectiveness of emergency contraceptive pills in women weighing over 165 pounds. Health Canada had evaluated new data from Laboratoire HRA Pharma and asked companies to add new warnings to product

packages of Next Choice (Cobalt Pharmaceuticals Company), Norlevo (Laboratoire HRA Pharma), Option 2 (Perrigo International) and Plan B (Teva Women's Health Inc.) advising that these pills are less effective in women weighing 165 to 176 pounds (75-80 kg), and are not effective in women over 176 pounds (80 kg). All these pills contain levonorgestrel. Women who weigh 165 pounds or more are advised to ask a health professional, such as a doctor or pharmacist, for advice on alternative methods of emergency contraception.

In Hong Kong, there are 28 registered emergency contraceptive medicines containing levonorgestrel and they are prescription only medicines. Review of emergency contraceptives had been started by EMA and Health Canada to assess whether increased bodyweight or body mass index reduce the efficacy of these medicines in preventing an unintended pregnancy and had been reported in Drug News Issue No. 52. In view of Health Canada's latest recommendation, a letter to healthcare professionals to draw their attention was issued on 27 March 2014, and the matter will be discussed in the meeting of the Registration Committee.

### **Singapore: Missing administration port protector from 17 Baxter intravenous solution**

It was noted from the HSA website on 27 March 2014 that Baxter Healthcare alerted healthcare professionals of a possible defect involving missing port protectors from its range of 17 intravenous products. Baxter intravenous products with missing port protectors should not be used and any adverse events associated with the use of defective Baxter intravenous products should be reported to Baxter.

In Hong Kong, there are various intravenous solutions registered by Baxter. Regarding the above issue, Baxter had informed DH and issued a letter to healthcare professionals on 3 December 2013 to advise them not to use Baxter flexible solution containers if the administration port protector is not in place prior to use. Besides, Baxter is applying the change of product inserts of the products to include such information. DH will keep vigilance against any safety updates of the products.

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### **Canada: Association of mirtazapine with QT Prolongation/Torsades de Pointes**

On 28 March 2014, Health Canada announced new warnings for mirtazapine regarding post marketing cases of QT prolongation and torsades de pointes reported with the use of mirtazapine. Most cases occurred in association with drug overdose or in patients with other risk factors for QT prolongation, including concomitant use of QT prolonging medications. The Product Monograph in Canada had been updated to include this information and to advise caution in patients with risk factors such as known cardiovascular disease, family history of QT prolongation and concomitant use of QT

prolonging medications. Healthcare professionals are advised to monitor vital signs and cardiac rhythm in the management of mirtazapine overdose.

In Hong Kong, there are 24 registered pharmaceutical products containing mirtazapine. They are prescription only medicines indicated for the treatment of depression. In view of Health Canada's announcement, a letter to inform healthcare professionals on the warnings announced by Health Canada was issued on 31 March 2014 and the matter will be discussed in the meeting of Registration Committee.

## Drug Incident

### **Public urged not to buy or consume slimming product with undeclared and banned Western drug ingredients**

On 26 March 2014, DH appealed to members of the public not to buy or consume a slimming product called LAMI as it is suspected to contain undeclared and banned drug ingredients that might be dangerous to health.

DH was notified by Hospital Authority (HA) about a 35-year-old female patient who developed psychotic symptoms including abnormal behaviour and auditory hallucination. It was found that she had a history of consuming the above slimming product which she had bought locally. According

to HA, samples of the product provided by the patient were found to contain the Part I poisons sibutramine and spironolactone

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. Spironolactone is a prescription drug used in the management of heart failure and should only be used under supervision of a doctor. Side effects include headache, gastrointestinal disturbances, mental confusion, hyponatraemia and hyperkalaemia.

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-XXXXXX". The products mentioned in the above incidents were not registered pharmaceutical products under the Ordinance in Hong Kong. Their safety, quality and efficacy cannot be guaranteed. Members of the public were exhorted not to use products of unknown or doubtful composition. They should stop using the aforementioned products immediately if they had them in their possession and to consult healthcare professionals if they felt unwell after taking the products. The products should be destroyed or disposed properly, or submitted to the Department's Drug Office during office hours.

## *Useful Contact*

### Drug Complaint:

Tel: 2572 2068

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E-mail: [pharmgeneral@dh.gov.hk](mailto:pharmgeneral@dh.gov.hk)

### Adverse Drug Reaction (ADR) Reporting:

Tel: 2319 2920

Fax: 2186 9845

E-mail: [adr@dh.gov.hk](mailto: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,  
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***The purpose of Drug News is to provide healthcare professionals with a summary of local and overseas drug safety news released. Healthcare professionals are advised to keep update with the information and provide corresponding advice or therapeutic measure to patients and public.***