



Drug News

藥物情報

Issue Number 76

This is a monthly digest of local and overseas drug safety news released by the Drug Office of the Department of Health in February 2016 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

EU: EMA concludes defective device in ROCKET study does not impact Xarelto's safety

On 5 February 2016, the European Medicines Agency (EMA) has concluded that a defect with the international normalised ratio (INR) device used in the ROCKET study does not change its conclusions on the overall safety or benefit-risk balance of Xarelto (rivaroxaban).

The ROCKET study was the main clinical trial underpinning the use of this anti-clotting medicine in patients with non-valvular atrial fibrillation (irregular heartbeat). This means that Xarelto can continue to be used as before, in line with the current prescribing information.

In the study, which compared Xarelto with warfarin, the INR device was used to measure blood clotting in patients taking warfarin. Because of the defect, there were concerns that the INR device could have provided lower INR values in some patients in the warfarin group. The lower values could in turn have led investigators to give too high a dose in the warfarin group, increasing their risk of bleeding and so giving a false impression of the comparative safety of Xarelto.

After further analyses of the ROCKET study data taking into account the defect in the INR device, EMA's Committee for Medicinal Products for Human Use (CHMP) concluded that any incorrect measurements obtained with the defective device would have had only a marginal effect on the study results, and the safety of Xarelto remains unchanged. In addition, data from other large studies confirmed

the comparative safety of the medicine and showed similar rates of bleeding in their warfarin groups.

The CHMP therefore considered that the benefit-risk balance of Xarelto in patients with non-valvular atrial fibrillation remains unchanged.

EMA started investigating this issue as soon as it was informed of the defect in the INR device by the marketing authorisation holder of Xarelto, Bayer Pharma AG, in September 2015.

The CHMP assessment report with detailed information on the analyses performed will be published shortly on EMA's website.

In Hong Kong, Xarelto Tab 10mg (HK-57861), Xarelto Tab 15mg (HK-61396) and Xarelto Tab 20mg (HK-61395) are pharmaceutical products registered by Bayer Healthcare Ltd, and are prescription only medicines. As on 20 April 2016, the Department of Health (DH) has received ten adverse drug reaction (ADR) cases related to the products. DH will continue to remain vigilant on the safety of medicines containing rivaroxaban.

EU: Start of review of inhaled corticosteroids for chronic obstructive pulmonary disease - Known risk of pneumonia to be examined in detail

On 12 February 2016, the EMA has started a review of inhaled corticosteroid-containing medicines used to treat chronic obstructive pulmonary disease (COPD). COPD is a long-term inflammatory disease of the lungs in which the airways and air sacs in the lungs become damaged

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or blocked. Corticosteroids are widely used in the European Union (EU) to treat COPD and are usually taken by inhalation using an inhaler device.

The review of inhaled corticosteroid-containing medicines has been requested by the European Commission to evaluate the risk of pneumonia (inflammation of the lungs) when these medicines are used for COPD. The risk of pneumonia with these medicines is known and was first identified in 2007 when a study showed that patients treated with an inhaled corticosteroid, fluticasone, were at higher risk of developing pneumonia than those given placebo (dummy treatment). Since then, new studies of individual inhaled corticosteroids and combined study results (meta-analyses) on the class of inhaled corticosteroids have provided further data on the risk of pneumonia and it was considered necessary that a thorough review be performed to further characterise this risk.

EMA will now review all available data on the risk of pneumonia with inhaled corticosteroids for COPD and consider the need to update the existing prescribing advice across the EU.

Corticosteroids, also known as steroids, are anti-inflammatory medicines used for a wide range of conditions. They are similar to natural hormones normally produced by the adrenal glands (two small glands located above the kidneys). When taken by inhalation, they attach to receptors in the airways and cause a reduction in lung inflammation, which makes breathing easier. They are usually taken via inhalers which either contain a corticosteroid alone or a corticosteroid in combination with another medicine (such as a long-acting beta₂ agonist). Beclomethasone, budesonide, flunisolide, fluticasone propionate and fluticasone furoate are corticosteroids authorised and marketed as inhalation formulations for use in COPD.

In Hong Kong, inhaled corticosteroids are registered pharmaceutical products, including 13 beclomethasone products, 18 budesonide products, 29 fluticasone propionate products and 2 fluticasone furoate products, while flunisolide is not registered. All these registered products are prescription only medicines, except beclomethasone in aerosol dispensers which are pharmacy only medicines. As on 20 April 2016, DH has received two ADR cases on fluticasone

furoate, but none of them was related to pneumonia after using the product. In view of the start of the EMA review to consider the need to update the existing prescribing advice, DH remains vigilant on the conclusion of the review, and any safety updates from other overseas drug regulatory authorities.

UK: Spironolactone and renin-angiotensin system drugs in heart failure: risk of potentially fatal hyperkalaemia

On 17 February 2016, the Medicines and Healthcare products Regulatory Agency (MHRA) advised that monitoring of blood electrolytes is essential in patients coprescribed a potassium-sparing diuretic and an angiotensin converting enzyme inhibitor (ACEi) or an angiotensin receptor blocker (ARB) for heart failure.

Spironolactone is indicated in patients with congestive heart failure. It is a competitive aldosterone antagonist that increases sodium excretion while reducing potassium loss at the distal renal tubule. This mechanism of action means that hyperkalaemia can occur, particularly in patients with impaired renal function. Spironolactone should not be used in patients with severe renal impairment or pre-existing hyperkalaemia.

ACEi are mainly indicated in patients with hypertension or heart failure. ARBs are also indicated in hypertension and some are also indicated in heart failure. Recognised side effects of treatment with an ACEi or ARB include renal dysfunction and an increase in serum potassium. Risk factors for hyperkalaemia, such as renal insufficiency and diabetes mellitus, are more common in patients who require treatment with ACEi or ARB. Dehydration may also increase the risk of renal dysfunction leading to hyperkalaemia. Hyperkalaemia has been estimated to occur in between 1 in 100 and 1 in 1000 patients who take an ACEi or ARB.

A recent coroner's case reported to MHRA described a case of fatal hyperkalaemia in a patient with heart failure, diabetes, and chronic renal failure who was being treated with several medicines including spironolactone. A low-dose ACEi was subsequently added for treatment of

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increased blood pressure. A few days later, the patient was admitted to hospital with severe hyperkalaemia and acute-on-chronic renal failure and subsequently died.

The recent increase in reporting has coincided with the outcome of a European review on dual blockade therapy with ACEi and ARB. This review concluded that combination use of ACEi and ARB (which both inhibit the renin-angiotensin system) is not recommended because of an increased risk of hyperkalaemia, hypotension, and impaired renal function. The recent increase in number of UK cases reported could reflect an increase in coadministration of spironolactone and ACEi or ARB, or it could represent stimulated reporting due to increased awareness of the risks.

In Hong Kong, there are 9 registered pharmaceutical products containing spironolactone, 153 ACEi (including 1 containing cilazapril, 43 containing enalapril maleate, 45 containing lisinopril, 8 containing perindopril arginine, 15 containing perindopril erbumine, 13 containing ramipril, 16 containing captopril, 2 containing imidapril hydrochloride, 3 containing trandolapril, 3 containing benazepril hydrochloride and 4 containing zofenopril calcium) and 258 ARB (including 20 containing candesartan, 80 containing valsartan, 4 containing azilsartan, 2 containing eprosartan, 63 containing losartan, 23 containing telmisartan, 52 containing irbesartan, 14 containing olmesartan). All are prescription only medicines. As on 20 April 2016, DH has received one ADR case on spironolactone, but it is not related to hyperkalemia due to co-administration of spironolactone and ACEi/ARB. In view of the MHRA's announcement, letters to inform local healthcare professionals were issued on 18 February 2016. DH remains vigilant on any safety updates of the drugs combination and actions taken by overseas regulatory authorities for consideration of any action deemed necessary.

Taiwan: Announcement on matter related to update of Chinese package insert of medicinal products containing recombinant human tissue-type plasminogen activator (rt-PA)

After soliciting relevant information with clinical literature reports for overall assessment on medicinal products containing recombinant human tissue-type

plasminogen activator (rt-PA), the Taiwan Food and Drug Administration (FDA) announced on its website on 23 February 2016 that contents of (1) Contraindications and (2) The warnings and precautions of the Chinese package inserts of these products should be revised. The details of the requirement are at the following website: <http://www.fda.gov.tw/TC/newsContent.aspx?id=19629&chk=ae998a67-3d8c-4311-ba6d-c10459331f6c¶m=pn#.VxihP8tf2U1>

In Hong Kong, there are two registered oral pharmaceutical products containing rt-PA/alteplase, namely Actilyse Lyophilised Pdr for IV Inf 50mg (HK-30511) and Actilyse Lyophilised Pdr for IV Inj 20mg (HK-37894) registered by Boehringer Ingelheim (HK) Ltd. Both are prescription only medicines. The package insert of the products has included information that Actilyse is not suitable for use in elderly over 80 years old for acute stroke. As on 20 April 2016, DH has not received any ADR case related to rt-PA. In view of the announcement of the Taiwan FDA, the matter will be discussed by the Registration Committee of the Pharmacy and Poisons Board.

EU: EMA confirms recommendations to minimise risk of brain infection progressive multifocal leukoencephalopathy (PML) with Tysabri

On 26 February 2016, the EMA has completed its review of the known risk of PML with the multiple sclerosis medicine Tysabri (natalizumab), and has confirmed initial recommendations aimed at minimising this risk.

PML is a rare brain infection caused by John Cunningham (JC) virus. This virus is very common in the general population and is normally harmless; however, it can lead to PML in persons whose immune system is weakened. The most common symptoms of PML are progressive weakness, speech and communication difficulties, vision changes, and sometimes changes in mood or behaviour. PML is a very serious condition that may result in severe disability or death.

Recent studies suggest that early detection and treatment of PML when the disease is asymptomatic (is still in the initial stages and

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shows no symptoms) may improve patients' outcomes. Asymptomatic cases of PML can be detected on MRI scans, and experts in the field of MRI and multiple sclerosis agree that simplified MRI protocols (which allow for shorter procedures, and also limit the burden for patients undergoing the scans) permit the identification of PML lesions. All patients taking Tysabri should undergo full MRI scans at least once a year, but on the basis of the new data EMA now recommends that for patients at higher risk of PML more frequent MRI scans (e.g. every 3 to 6 months) performed using simplified protocols should be considered. If lesions suggestive of PML are discovered, the MRI protocol should be extended to include 'contrast-enhanced T1-weighted MRI', and testing the spinal fluid for the presence of JC virus should be considered.

New data from large clinical studies also suggest that, in patients who have not been treated with immunosuppressants (medicines that reduce the activity of the immune system) before starting Tysabri, the blood level of antibodies against JC virus ('antibody index') relates to the level of risk for PML.

In Hong Kong, Tysabri Concentrate for Solution for Infusion 300mg (HK-61519) is a pharmaceutical product registered by UCB Pharma (Hong Kong) Limited, and is a prescription only medicine. News on the start of review of Tysabri was previously issued by the EMA, and was reported in the Drug News Issue No. 72. Letters to inform local healthcare professionals was issued on 15 February 2016. The local package insert of the product has already included the warning on PML. As on 20 April 2016, DH has not received any ADR case related to the product. In view of the confirmation of the EMA's review with updated recommendations to minimise the risk of PML, the matter will be discussed by the Registration Committee of the Pharmacy and Poisons Board.

EU: EMA confirms recommendations to minimise ketoacidosis risk with SGLT2 inhibitors for diabetes

On 26 February 2016, the EMA has confirmed recommendations to minimise the risk of diabetic ketoacidosis in patients taking SGLT2 inhibitors (a class of type 2 diabetes medicines).

Diabetic ketoacidosis is a serious complication of diabetes caused by low insulin levels. Rare cases of this condition, including life-threatening ones, have occurred in patients taking SGLT2 inhibitors for type 2 diabetes and a number of these cases have been atypical, with patients not having blood sugar levels as high as expected.

An atypical presentation of diabetic ketoacidosis can delay diagnosis and treatment. Healthcare professionals should therefore consider the possibility of ketoacidosis in patients taking SGLT2 inhibitors who have symptoms consistent with the condition even if blood sugar levels are not high.

Following a review of the cases, EMA has recommended updating the product information of SGLT2 inhibitors to list diabetic ketoacidosis as a rare adverse reaction (affecting up to 1 in 1,000 patients).

Patients taking these medicines should be aware of the symptoms of diabetic ketoacidosis, including rapid weight loss, nausea or vomiting, stomach pain, excessive thirst, fast and deep breathing, confusion, unusual sleepiness or tiredness, a sweet smell to the breath, a sweet or metallic taste in the mouth, or a different odour to urine or sweat. Patients should contact a doctor or the nearest hospital straightaway if they have any of these symptoms.

If diabetic ketoacidosis is suspected or confirmed, treatment with SGLT2 inhibitors should be stopped immediately and should not be re-started unless another cause for the ketoacidosis is identified and resolved.

Healthcare professionals should exercise caution with SGLT2 inhibitors in patients with risk factors for ketoacidosis and inform patients of these factors. These include low insulin-producing capacity in the pancreas, a sudden drop in a patient's insulin dose, increased insulin requirement (due to illness, surgery or alcohol abuse) or conditions that can restrict food intake or lead to severe dehydration.

In addition, EMA recommends temporarily stopping SGLT2 inhibitors in patients who are

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undergoing major surgery or are in hospital due to serious illness.

In Hong Kong, there are two registered pharmaceutical products containing dapagliflozin, namely Forxiga Tablets 5mg (HK-63301) and 10mg (HK-63302) registered by AstraZeneca HK Ltd (Astra); two registered products containing canagliflozin, namely Invokana Tablets 100mg (HK-63499) and 300mg (HK-63500) registered by Johnson & Johnson (HK) Ltd (J&J); and six registered products containing empagliflozin, namely Jardiance Tablets 10mg (HK-64095) and 25mg (HK-64096), Jardiance Duo Tablets 12.5mg/850mg (HK-64240), 5mg/850mg (HK-64241), 12.5mg/1000mg (HK-64242) and 5mg/1000mg (HK-64243) registered by Boehringer Ingelheim (HK) Ltd (Boehringer). All these products are prescription only medicines. Related news was previously issued by various overseas drug regulatory authorities, and was reported in the Drug News Issues No. 67 and 74.

On 9 July 2015, 10 July 2015 and 14 December 2015, J&J, Astra and Boehringer notified DH respectively that they had issued letters to inform local healthcare professionals on the risk of diabetic ketoacidosis with SGLT2 inhibitors. As on 20 April 2016, DH has received two ADR cases of ketoacidosis after taking SGLT2 inhibitors, one case involved dapagliflozin and the other case involved canagliflozin. As previously reported, the matter will be discussed by the Registration Committee of the Pharmacy and Poisons Board.

Drug Recall

Batch recall of Normosol-M & 5% Dextrose Injection (HK-32659)

On 2 February 2016, DH endorsed a licensed drug wholesaler, Pfizer Corporation Hong Kong Ltd (Pfizer), to recall one batch (batch number: 56-853-FW) of Normosol-M & 5% Dextrose Injection (Hong Kong registration number: HK-32659) from the market due to a printing error.

DH was notified by Pfizer on 2 February 2016 that a complaint was received by Pfizer involving a printing error on the expiry date printed on the package of the product. The expiry date was mistakenly printed as 1 AUG 1017 instead of 1 AUG 2017. As a precautionary measure, Pfizer voluntarily recalled the above affected batch from the market.

Normosol-M & 5% Dextrose Injection (containing Dextrose and other electrolytes) is an over-the-counter medicine indicated for maintenance of body fluid and electrolytes.

According to Pfizer, about 3,394 bags (each bag containing 1,000ml) from the affected batch had been supplied to the 4 private hospitals and one private clinic. As on 20 April 2016, DH had not received any ADR case related to the affected batch of this pharmaceutical product. DH closely monitored the incident. A notice was released on the website of Drug Office on the same day to alert the public of the recall.

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,
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.