



*This is a monthly digest of local and overseas drug safety news released by the Drug Office of the Department of Health in June 2017 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: PRAC concludes there is no evidence of a change in known risk of neutropenic enterocolitis with docetaxel**

On 9 June 2017, the European Medicines Agency (EMA)'s Pharmacovigilance Risk Assessment Committee (PRAC) has concluded that there is no evidence of a change in the known risk of neutropenic enterocolitis after treatment with docetaxel, a cancer medicine. Neutropenic enterocolitis is a serious inflammatory condition of the intestine which may occur in up to 1 in 1,000 cancer patients taking the medicine.

Having considered available data on docetaxel, the Committee concluded that the recent rise in reporting of the condition observed in France could be due to an increased awareness among healthcare professionals. Reporting rates in the European Union (EU) as a whole do not provide any evidence of an increase in the incidence of neutropenic enterocolitis. Neutropenic enterocolitis remains a rare side effect of docetaxel and will continue to be under routine monitoring and evaluated during periodic reviews of docetaxel medicines.

In Hong Kong, there are 28 registered pharmaceutical products containing docetaxel. All these products are prescription only medicines. Related news was previously issued by EMA, and was reported in the Drug News Issue No. 89. As on 18 July 2017, the Department of Health (DH) has received 9 cases of adverse drug reaction (ADR), but none of them were related to neutropenic enterocolitis. DH will remain vigilant on safety update of docetaxel issued by other overseas drug regulatory authorities.

### **UK: Denosumab (Prolia, Xgeva): reports of osteonecrosis of the external auditory canal**

On 21 June 2017, the Medicines and Healthcare products Regulatory Agency (MHRA) of the United Kingdom (UK) announces that osteonecrosis of the external auditory canal has been reported with denosumab. Denosumab is known to be associated with osteonecrosis of the jaw. Worldwide, 5 reports of osteonecrosis of the external auditory canal have now been received for patients treated with 60 mg denosumab for osteoporosis. The underlying possible pathological mechanism is considered to be similar to that for denosumab-related osteonecrosis of the jaw. The number of cases of osteonecrosis of the external auditory canal in association with denosumab is low compared with those of osteonecrosis of the jaw.

Denosumab is a human monoclonal IgG2 antibody. Denosumab 60mg solution for injection (Prolia) is indicated for the treatment of osteoporosis in postmenopausal women and in men at increased risk of fractures, and for the treatment of bone loss associated with hormone ablation in men with prostate cancer at increased risk of fractures in UK. Denosumab 120mg solution for injection (Xgeva) is indicated for the prevention of skeletal-related events (pathological fracture, radiation to bone, spinal cord compression, or surgery to bone) in adults with bone metastases from solid tumours, and for the treatment of adults and skeletally mature adolescents with giant cell tumour of bone that is unresectable or where surgical resection is likely to result in severe morbidity in UK.

The product information for all denosumab-

# Safety Update

containing products in UK is being revised to include a warning on the risk of osteonecrosis of external auditory canal. Healthcare professionals are advised:

- the possibility of osteonecrosis of the external auditory canal should be considered in patients receiving denosumab who present with ear symptoms including chronic ear infections or in those with suspected cholesteatoma;
- possible risk factors include steroid use and chemotherapy, with or without local risk factors such as infection or trauma;
- to advise patients to report any ear pain, discharge from the ear, or an ear infection during denosumab treatment; and
- to report cases of osteonecrosis of any bone suspected to be associated with denosumab or any other medicine on a Yellow Card.

In Hong Kong, there are 3 registered pharmaceutical products containing denosumab, namely Prolia Solution for Injection in Pre-filled Syringe 60mg/ml (USA) (HK-60588), Prolia Solution for Injection in Pre-filled Syringe 60mg/ml (The Netherlands) (HK-60589) and Xgeva Solution for Injection 120mg (HK-61163). All products are registered by Amgen Asia Holding Limited (Amgen), and are prescription only medicines. As on 18 July 2017, DH has received 9 cases of ADR related to denosumab, including 2 cases of osteonecrosis. In February 2016, the Registration Committee of the Pharmacy and Poisons Board (the Registration Committee) had decided that warnings on the risk of osteonecrosis of the jaw should be included in the sales pack labels and/or package inserts of products containing denosumab. Amgen had submitted applications to update the package inserts. The applications have been reviewed and the updated package inserts will include the safety information on the risks of osteonecrosis of the jaw. In light of the above MHRA's announcement on osteonecrosis of the external auditory canal, DH issued a letter to update local healthcare professionals to draw their attention on the above risk on 22 June 2017 and the matter will be discussed by the Registration Committee.

## **UK: Brimonidine gel (Mirvaso): risk of systemic cardiovascular effects; not to be applied to damaged skin**

On 21 June 2017, MHRA of UK announces that systemic cardiovascular effects including bradycardia, hypotension, and dizziness have been reported after application of brimonidine gel. A routine European review identified post-marketing reports, including a small number of Yellow Cards, consistent with systemic (central)  $\alpha$ -2 adrenergic effects, including bradycardia, hypotension (including orthostatic hypotension), and dizziness. Some patients required hospitalisation. Dizziness is reported to occur uncommonly, with an estimated frequency of less than 10 in 1000 patients using brimonidine gel. Hypotension and bradycardia are reported to occur rarely, with an estimated frequency of less than 1 in 1000 patients. In approximately 30% of the cases most strongly suggestive of a cardiovascular effect, events occurred following application of brimonidine gel after laser therapy to the skin.

Brimonidine (Mirvaso) is a topical gel indicated for the symptomatic treatment of facial erythema of rosacea in adults in UK. It is an  $\alpha$ -2 adrenergic agonist.

Healthcare professionals are advised:

- cases of bradycardia, hypotension (including orthostatic hypotension), and dizziness after application of brimonidine gel have been reported, some of which required hospitalization;
- some cases were associated with application of brimonidine gel after laser procedures to the skin, which possibly caused increased absorption of the gel; and
- to warn patients not to apply brimonidine gel to irritated or damaged skin, including after laser therapy to the skin.

In Hong Kong, Mirvaso Gel 0.33% (HK-63413) is a pharmaceutical product containing brimonidine. The product is registered by Galderma Hong Kong Limited, and is a prescription only medicine. As on 18 July 2017, DH has not received any case of ADR related to brimonidine. In light of the above MHRA's announcement, DH issued a letter to update local healthcare professionals to draw their attention on the above risk on 22 June 2017. DH

## Safety Update

will remain vigilant on safety update of the product and any change in product information issued by overseas drug regulatory authorities.

### **Singapore: HSA updates on the phasing-out of lysozyme-containing products as therapeutic products**

On 27 June 2017, the Health Sciences Authority (HSA) of Singapore has conducted a re-evaluation of the benefit-risk profile of lysozyme and concluded that it has failed to show efficacy. As such, HSA will be phasing out the use of lysozyme in therapeutic products in Singapore. Currently, lysozyme-containing products are approved as an expectorant and mucolytic for chronic sinusitis, as well as treatment for bleeding.

The re-evaluation was undertaken following the voluntary cancellation of the product Neuzym by the registrant (Eisai) in Singapore in March 2016, due to the failure of recent post-marketing studies to show statistical significant differences in the efficacy of lysozyme compared to placebo. HSA concluded likewise that evidence from the post-market clinical studies as well as published

literature as on 27 June 2017 had failed to show efficacy of lysozyme. While lysozyme has a long history of use in Singapore since 1989 with no significant safety concern, the lack of efficacy rendered its use as a therapeutic product unjustifiable. Nonetheless, the lack of efficacy for therapeutic use does not preclude the use of lysozyme in other categories of health products such as health supplements.

Therefore, lysozyme-containing products will be de-registered as therapeutic products in Singapore. Considering the long history of use of lysozyme in Singapore and the acceptable safety profile, currently registered lysozyme-containing products will be allowed a grace period until 31 December 2018, before the products are removed from the Register of Therapeutic Products in Singapore.

In Hong Kong, there are 257 registered pharmaceutical products containing lysozyme, including 51 single-ingredient products and 206 multiple-ingredient products. As on 18 July 2017, DH has not received any case of ADR related to lysozyme. The matter will be discussed by the Registration Committee.

## Drug Incident

### **Man arrested for suspected illegal sale of nicotine-containing liquids for electronic cigarettes**

On 20 June 2017, a joint operation was conducted by DH and the Police in Wong Tai Sin resulting in the arrest of a 22-year-old man for selling illegally three nicotine-containing liquids, namely "JAM MONSTER", "NINJA MAN" and "Crush FRUITS". All of the liquid products are intended for use with electronic nicotine delivery systems, commonly known as electronic cigarettes.

Acting upon a public complaint, DH found that the above products were offered for sale on a social networking website. Samples of the products were then purchased for laboratory analysis. Test results from the Government Laboratory revealed that all samples contained Part 1 poison nicotine. During the operation, the seller was arrested by the Police for suspected illegal sale of Part 1 poison and unregistered pharmaceutical products.

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

Smokers are advised to quit smoking for their own and others' health. They are encouraged to make use of smoking cessation services through DH's Integrated Smoking Cessation Hotline (1833 183). Information on smoking cessation can also be obtained from DH's Tobacco Control Office website ([www.tco.gov.hk](http://www.tco.gov.hk)).

A notice was released on the website of Drug Office on 20 June 2017 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](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](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](mailto:pharmgeneral@dh.gov.hk)

### **Adverse Drug Reaction (ADR) Reporting:**

Tel: 2319 2920

Fax: 2319 6319

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,  
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.***