Drug News
藥物情報

Issue Number 93

This is a monthly digest of local and overseas drug safety news released by the Drug Office of the Department of Health in July 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 recommends that injectable methylprednisolone products containing lactose must not be given to patients allergic to cow's milk proteins. Companies to replace all current formulations containing lactose with lactose-free formulations

On 7 July 2017, the European Medicines Agency (EMA)'s Pharmacovigilance Risk Assessment Committee (PRAC) has recommended that injectable methylprednisolone medicines containing lactose, which potentially contain traces of cow's milk proteins, must not be used in patients with a known or suspected allergy to the proteins in cow's milk. In addition, patients being treated for an allergic reaction with methylprednisolone should have their treatment stopped if their symptoms worsen or they develop new symptoms.

These recommendations follow a review which found that lactose derived from cow's milk may introduce traces of cow's milk proteins into the medicine which can trigger reactions in patients allergic to these proteins. This is of particular concern in patients already being treated for an allergic reaction as they are more prone to developing new allergic reactions. In this case it may be difficult to determine whether the patient's symptoms are due to a new allergic reaction caused by methylprednisolone products containing lactose or due to a worsening of the original condition. This may lead to additional doses being given which will further worsen the patient's condition.

PRAC concluded that there is no level of cow milk proteins that can be considered safe for these medicines when used to treat severe allergic reactions. Considering that methylprednisolone is used for the treatment of severe allergic reactions in an emergency setting where details of the patients' known allergies may not always be known, PRAC recommended that the most effective way of minimising any risks is to remove cow's milk proteins from the preparation. The Committee therefore asked companies to take steps by middle of 2019 to replace current formulations containing cow's milk proteins with formulations that do not contain these proteins.

In the meantime, the product information will be revised to reflect that injectable methylprednisolone products containing lactose must not be given to patients allergic to cow's milk proteins. In addition, the vial and packaging of these medicines will be clearly marked with a warning against use in patients with cow's milk allergy.

In Hong Kong, there are 8 registered pharmaceutical products which are injectable methylprednisolone. Amongst them, only Solu Medrol 40mg Steril Mix-O/Act-O Vial (HK-00466) contains both methylprednisolone and lactose, which is registered by Pfizer Corporation Hong Kong Limited and is a prescription only medicine.

In light of the above EMA's announcement, the Department of Health (DH) issued a letter to inform local healthcare professionals on the new warnings on 10 July 2017. The matter will also be discussed by the Registration Committee of the Pharmacy and Poisons Board (Registration Committee).

UK: Bendamustine (Levact): increased mortality observed in recent clinical studies in off-label use; monitor for opportunistic infections, hepatitis B reactivation

On 20 July 2017, the Medicines and Healthcare products Regulatory Agency (MHRA) of the United Kingdom (UK) announced that in clinical trials of non-approved combination therapies, bendamustine was associated with increased mortality and an unfavourable safety profile when used in combination with rituximab or obinutuzumab. Deaths were mainly due to infections including bacterial (sepsis, pneumonia) and opportunistic infections such as Pneumocystis jirovecii pneumonia, varicella zoster virus, and cytomegalovirus infection. Some fatal cardiac, neurological, and respiratory toxicities were also reported.

Regarding post-marketing data, a recent European review has suggested that the risk of opportunistic infections with bendamustine treatment may be greater than previously recognised. Infections include bacterial (sepsis, pneumonia) and opportunistic infections such as Pneumocystis jirovecii pneumonia, varicella zoster virus, and cytomegalovirus infection. Both the frequency and outcome of infections seem to be highly variable and dependent on the clinical setting. Reactivation of hepatitis B virus (HBV) in chronic carriers of the virus has been reported after bendamustine. Some cases resulted in acute hepatic failure or a fatal outcome.

Healthcare professionals are advised:

- to advise patients to report promptly new signs of infection, including fever or respiratory symptoms, and consider discontinuing bendamustine if there are signs of opportunistic infections;
- to monitor patients for opportunistic infections as well as cardiac, neurological, and respiratory adverse events;
- HBV reactivation has also been reported; monitor known carriers of HBV for signs and symptoms of active HBV infection;
- increased mortality (mainly due to opportunistic infections) was observed in recent clinical studies when bendamustine was used in combination treatment outside the approved indications.

In Hong Kong, there are 2 registered pharmaceutical products containing bendamustine, namely Treanda for Inj 100mg (HK-59067) and Treanda for Injection 25mg (HK-62300). These products are registered by Ivax Asia Ltd, and are prescription-only medicines. As on 16 August 2017, DH has received one case of adverse drug reaction (ADR) related to bendamustine, but it was not related to infection. DH issued a letter to inform local healthcare professionals of the above safety information on 21 July 2017 and DH will remain vigilant on safety update of bendamustine issued by other overseas drug regulatory authorities.

UK: Nivolumab (Opdivo▼), pembrolizumab (Keytruda▼): reports of organ transplant rejection

On 20 July 2017, MHRA announced that there have been reports of rejection of solid organ transplants in patients treated with nivolumab or pembrolizumab. Ipilimumab (Yervoy▼) may also interfere with immunosuppressive therapy, increasing the risk of graft rejection.

A European review of worldwide data concluded that nivolumab and pembrolizumab may increase the risk of rejection in organ transplant recipients. The review assessed all cases received up to November 2016 and identified 9 patients who had transplant rejection after receiving nivolumab and pembrolizumab. Of the 5 patients receiving nivolumab, 3 had kidney transplant rejection, 1 had corneal transplant rejection, and 1 had skin graft rejection. Four patients receiving pembrolizumab had kidney transplant rejection; 2 patients were diagnosed after biopsy. In 2 of the 9 reports of rejection, patients started treatment with ipilimumab before receiving nivolumab or pembrolizumab. Ipilimumab is known to increase the risk of graft rejection.

Healthcare professionals are advised:

- rejection of solid organ transplants, including renal and corneal grafts, has been reported in the post-marketing setting in patients treated with programmed death receptor 1 (PD-1) inhibitors;
- consider the benefit of treatment with nivolumab or pembrolizumab versus the risk of possible organ transplant rejection for each patient;

- some cases of rejection occurred in association with ipilimumab, which carries a warning that it may interfere with immunosuppressive therapy, resulting in an increased risk of graft rejection.

In Hong Kong, there are 2 pharmaceutical products containing nivolumab, namely Opdivo Concentrate for Solution for Infusion 40mg/4ml (HK-64231) and Opdivo Concentrate for Solution for Infusion 100mg/10ml (HK-64232) which are registered by Bristol-Myers Squibb Pharma (HK) Ltd, 2 products containing pembrolizumab, namely Keytruda Solution for Injection 100mg/4ml (HK-64228) and Keytruda Powder for Injection 50mg (HK-64229) which are registered by Merck Sharp & Dohme (Asia) Ltd, and 2 products containing ipilimumab, namely Yervoy Concentrate for Solution for Infusion 50mg/10ml (HK-63494) and Yervoy Concentrate for Solution for Infusion 200mg/40ml (HK-63495) which are registered by Bristol-Myers Squibb Pharma (HK) Ltd. All of the above products are prescription-only medicines.

As on 16 August 2017, DH has received 28 cases of ADR related to nivolumab, 25 cases related to pembrolizumab and 8 cases related to ipilimumab, but none of them was related to organ transplant rejection. In view of MHRA's reports, DH issued a letter to inform local healthcare professionals of the above safety information on 21 July 2017. The matter will be discussed by the Registration Committee and DH will remain vigilant on safety update of the drugs issued by other overseas drug regulatory authorities.

EU: EMA's final opinion confirms restrictions on use of linear gadolinium agents in body scans. Recommendations conclude EMA's scientific review of gadolinium deposition in brain and other tissues

On 21 July 2017, EMA of the European Union (EU) has concluded its review of gadolinium contrast agents, confirming recommendations to restrict the use of some linear gadolinium agents used in magnetic resonance imaging (MRI) body scans and suspend the authorizations of others.

The recommendations – confirmed by EMA's Committee for Medicinal Products for Human Use (CHMP) – follow a review that found that gadolinium deposition occurs in brain tissues following use of gadolinium contrast agents.

There is currently no evidence that gadolinium deposition in the brain has caused any harm to patients; however EMA has recommended restrictions for some intravenous linear agents in order to prevent any risks that could potentially be associated with gadolinium brain deposition.

The intravenous linear agents gadoxetic acid and gadobenic acid can continue to be used for liver scans because they are taken up in the liver and meet an important diagnostic need. In addition, gadopentetic acid given intra-articularly (into the joint) can continue to be used for joint scans because the dose of gadolinium used for joint injections is very low.

All other intravenous linear products (gadodiamide, gadopentetic acid and gadoversetamide) should be suspended in EU.

Another class of gadolinium agents known as macrocyclic agents (gadobutrol, gadoteric acid and gadoteridol) are more stable and have a lower propensity to release gadolinium than linear agents. These products can continue to be used in their current indications but in the lowest doses that enhance images sufficiently and only when unenhanced body scans are not suitable.

The suspensions or restrictions on linear agents can be lifted if the companies concerned provide evidence of new benefits in an identified patient group that outweigh the risk of brain deposition or if the companies can modify their products so they do not release gadolinium significantly or cause its retention in tissues.

EMA's scientific review of gadolinium deposition in brain and other tissues is now concluded. The final recommendations will be sent to the European Commission, which will issue a final legally binding decision applicable in all EU Member States.

Product	Type (formulation)	Recommendation
Artirem / Dotarem (*gadoteric acid*)	macrocyclic (i.v.)	maintain
Artirem / Dotarem (*gadoteric acid*)	macrocyclic (intra-articular)	maintain
Gadovist (*gadobutrol*)	macrocyclic (i.v.)	maintain
Magnevist (*gadopentetic acid*)	linear (intra-articular)	maintain
Magnevist (*gadopentetic acid*)	linear (i.v.)	suspend
Multihance (*gadobenic acid*)	linear (i.v.)	restrict use to liver scans
Omniscan (*gadodiamide*)	linear (i.v.)	suspend
Optimark (*gadoverset-amide*)	linear (i.v.)	suspend
Primovist (*gadoxetic acid*)	linear (i.v.)	maintain
Prohance (*gadoteridol*)	macrocyclic (i.v.)	maintain

Information for healthcare professionals

- Gadolinium deposition in the brain has been confirmed by mass spectrometry and increases in signal intensity in brain tissue.
- Data on stability, as well as *in vitro* and non-clinical studies, show that linear gadolinium agents release gadolinium from the ligand molecules to a greater extent than macrocyclic agents.
- No adverse neurological effects, such as cognitive or movement disorders, have been attributed to gadolinium deposition in the brain with any gadolinium agents.
- The marketing authorizations for the intravenous linear agents gadodiamide and gadoversetamide, as well as the intravenous formulation of the linear agent gadopentetic acid, are being suspended in EU.
- Two intravenous linear agents – gadoxetic acid and gadobenic acid – will remain available as these agents undergo hepatic uptake, and can be used for imaging poorly vascularised hepatic lesions, especially in delayed phase imaging, that cannot be adequately studied with other agents.
- Intra-articular formulations of the linear agent gadopentetic acid will continue to be available because the dose of gadolinium that is required for these scans is very low.
- All macrocyclic agents reviewed – gadobutrol, gadoteric acid and gadoteridol – will also remain available.
- Healthcare professionals should use gadolinium contrast agents only when essential diagnostic information cannot be obtained with unenhanced scans.
- Healthcare professionals should always use the lowest dose that provides sufficient enhancement for diagnosis.
- The product information for gadolinium contrast agents remaining on EU market will be updated accordingly.

In Hong Kong, there are 8 registered pharmaceutical products which are gadolinium contrast agents, and are prescription only medicines, including Magnevist Inj (HK-32608) containing meglumine gadopentetate, Omniscan Inj 0.5mmol/ml (HK-43493) containing gadodiamide, Gadovist Inj 1mmol/ml (HK-51750) and Gadovist Inj 1mmol/ml (Prefilled Syringe) (HK-57330) containing gadobutrol, Primovist Prefilled Syringe Inj 0.25mmol/ml (HK-54116) containing sodium gadoxetate, Dotarem Inj 377mg/ml (Vial) (HK-41578) and Dotarem Prefilled Syringes 377mg/ml (HK-41579) containing meglumine gadoterate, and MultiHance Inj 334mg (HK-57789) containing gadobenic acid (as meglumine gadobenate).

Related news was previously issued by various overseas drug regulatory authorities, and was reported in the Drug News Issue No. 69, 87 and 91. As on 16 August 2017, DH has received 7 cases of ADR in connection with gadolinium contrast agents: 2 cases on Omniscan, 3 cases on Dotarem, and 2 cases on Gadovist, but all these ADR cases were not related to gadolinium deposition in brain tissues. DH issued a letter to inform local healthcare professionals to draw their attention on the new warnings on 24 July 2017. The matter will be discussed by the Registration Committee.

Singapore: Keytruda (Pembrolizumab): Risk of Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis

It was noted from Health Sciences Authority (HSA) of Singapore website on 25 July 2017 that MSD Pharma (Singapore) Pte Ltd would like to inform healthcare professionals that cases of Stevens-Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN) have been reported in patients treated with Keytruda (pembrolizumab) in clinical trials and post-market setting. HSA has received 3 reports of SJS and 1 report of TEN, of which one had a fatal outcome in Singapore. Healthcare professionals are advised to counsel patients about the risks of SJS and TEN associated with Keytruda and the early symptoms of SJS and TEN. Keytruda treatment should be suspended if a patient is suspected to have SJS or TEN or permanently discontinue if SJS or TEN is confirmed. The Singapore package insert and patient medication guide have been updated to include SJS and TEN.

In Hong Kong, there are 2 pharmaceutical products containing pembrolizumab, namely Keytruda Solution for Injection 100mg/4ml (HK-64228) and Keytruda Powder for Injection 50mg (HK-64229), which are registered by Merck Sharp & Dohme (Asia) Ltd (MSD HK) and are prescription-only medicines.

Related news was previously issued by Health Canada, and was reported in the Drug News Issue No. 89. DH issued a letter to inform local healthcare professionals to draw their attention on 21 March 2017. As on 16 August 2017, DH has received 25 cases of ADR related to pembrolizumab, of which one case was related to TEN. In June 2017, the Registration Committee discussed the matter and noted that MSD HK had submitted application to update the package insert. This application has been reviewed and the updated package insert will include the safety information on the risks of SJS and TEN. DH will remain vigilant on safety update of the drug issued by other overseas drug regulatory authorities.

Australia: Gadolinium-based contrast agents for MRI scans: potential retention in the brain but no known adverse effects

On 28 July 2017, the Therapeutic Goods Administration (TGA) of Australia announced that TGA has reviewed recent information relating to the potential for small amounts of gadolinium to be retained in the brain, following use of gadolinium-based contrast agents during MRI scans. No harmful effects of gadolinium retention in the brain have been identified, but TGA is working with sponsors of these products to update their Product Information documents in Australia to reflect the new information.

Gadolinium-based contrast agents are injected into a patient's vein to enhance the quality of MRI scans of internal organs, blood vessels and tissues. MRI scans help health professionals to diagnose medical conditions. There are two types of gadolinium-based contrast agents - linear agents and macrocyclic agents. Published studies have found that linear gadolinium-based contrast agents appear to result in greater gadolinium retention in the brain than macrocyclic agents. TGA will continue to monitor this issue and take further action if necessary.

Healthcare professionals are advised to limit gadolinium-based contrast agent use to circumstances where the extra information provided by the contrast agent is necessary, and in those circumstances to use the lowest effective dose and carefully consider the choice of agent. TGA also recommends that healthcare professionals avoid repetitive scans using these contrast agents unless deemed clinically necessary.

In Hong Kong, there are 8 registered pharmaceutical products which are gadolinium-based contrast agents, and are prescription only medicines, including Magnevist Inj (HK-32608) containing meglumine gadopentetate, Omniscan Inj 0.5mmol/ml (HK-43493) containing gadodiamide, Gadovist Inj 1mmol/ml (HK-51750) and Gadovist Inj 1mmol/ml (Prefilled Syringe) (HK-57330) containing gadobutrol, Primovist Prefilled Syringe Inj 0.25mmol/ml (HK-54116) containing sodium gadoxetate, Dotarem Inj 377mg/ml (Vial) (HK-41578) and Dotarem Prefilled Syringes 377mg/ml (HK-41579) containing meglumine gadoterate, and MultiHance Inj 334mg (HK-57789) containing gadobenic acid (as meglumine gadobenate).

Related news was previously issued by various overseas drug regulatory authorities including the latest one released by the EMA on 21 July 2017 (on the above item 4). They were reported in the Drug News Issue No. 69, 87 and 91. DH issued a letter to

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inform local healthcare professionals to draw their attention on 24 July 2017. As on 16 August 2017, DH has received 7 cases of ADR in connection with gadolinium-based contrast agents: 2 cases on Omniscan, 3 cases on Dotarem, and 2 cases on Gadovist, but all these ADR cases were not related to gadolinium deposition in brain tissues. The matter will be discussed by the Registration Committee.

Singapore: Xgeva® (denosumab) Solution for Injection 120mg/vial - Risk of Multiple Vertebral Fractures (MVF) following treatment discontinuation

On 21 July 2017, HSA announced that Amgen Singapore Manufacturing Pte Ltd would like to inform healthcare professionals of the risk of Multiple Vertebral Fractures (MVF) that may occur following discontinuation of treatment with Xgeva® (denosumab), particularly in patients with risk factors such as osteoporosis or prior fractures. Cases of MVF, not due to bone metastases, have occurred rarely following discontinuation of Xgeva® in patients participating in ongoing clinical trials. These fractures had occurred in post-menopausal women with malignancies who had previous fractures or who had known osteoporosis. Healthcare professionals are advised to evaluate the individual patient's risk for vertebral fractures, following treatment discontinuation with Xgeva®. Patients should also be advised not to interrupt Xgeva® treatment without their physician's advice. The package insert for Xgeva® in Singapore will be updated to include warnings regarding the risk of MVF.

In Hong Kong, Xgeva Solution for Injection 120mg (HK-61163) is a pharmaceutical product registered by Amgen Asia Holding Limited, and is a prescription only medicine. As on 16 August 2017, DH has received 9 cases of ADR related to denosumab, but none of them was related to MVF. In light of the above HSA's announcement, DH issued a letter to inform local healthcare professionals to draw their attention on the above risk on 2 August 2017. The matter will also be discussed by the Registration Committee.

Drug Incident

DH raided retail shop for suspected illegal sale of unregistered pharmaceutical products

On 10 July 2017, DH raided a retail shop in Wan Chai for the suspected illegal sale and possession of unregistered pharmaceutical products labelled to contain Part 1 poison.

Acting upon a public complaint, it was found that the above shop was offering for sale five topical solutions labelled as containing the Part 1 poison tretinoin. They are:

1. RDL HYDROQUINONE TRETINOIN Babyface Solution 2;
2. RDL HYDROQUINONE TRETINOIN Babyface Solution 3;
3. maxi-peel tretinoin hydroquinone EXFOLIANT SOLUTION 1;
4. maxi-peel tretinoin hydroquinone EXFOLIANT SOLUTION 2; and
5. maxi-peel tretinoin hydroquinone EXFOLIANT SOLUTION 3.

Products containing tretinoin are prescription medicines which should only be used under doctor's advice or supplied at pharmacies under the supervision of a registered pharmacist upon a doctor's prescription.

Tretinoin is used topically for the treatment of acne. Its side-effects include erythema, dryness, peeling and photosensitivity. Sensitive individuals may experience oedema, blistering and crusting of the skin.

A notice was posted on the Drug Office website on 10 July 2017 to alert the public of the drug incident.

Drug Incident

DH raided retail shops for suspected illegal sale and possession of unregistered pharmaceutical products

On 17 July 2017, DH and the Police conducted a joint operation and raided three retail shops in Mong Kok for suspected illegal sale and possession of unregistered pharmaceutical products.

Acting upon a public complaint, DH found that the above retail shops had been offering for sale various unregistered pharmaceutical products, including Aveeno 1% Hydrocortisone Anti-itch Cream, Proctosedyl Ointment, Clinda-M and some products labelled in Japanese. Preliminary investigation indicated that the external preparations seized during the operation contained controlled ingredients including hydrocortisone, prednisolone, triamcinolone acetonide and clindamycin.

Hydrocortisone, prednisolone and triamcinolone acetonide are Part 1 poisons, which are steroidal drugs for treating inflammation. Inappropriate or excessive application of the drugs could cause skin problems. Clindamycin is an antibiotic used for treating bacterial infection and may cause side-effects such as hypersensitive reactions. Part 1 poisons and antibiotics should be used under the advice of medical practitioners.

A notice was posted on the Drug Office website on 17 July 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.
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,
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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.