Drug News
藥 物 情 報

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This is a monthly digest of local and overseas drug safety news released by the Drug Office of the Department of Health in May 2022 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: Amoxicillin and risk of aseptic meningitis

On 6 May 2022, Health Sciences Authority (HSA) advised healthcare professionals to consider the possibility of amoxicillin-associated aseptic meningitis in patients prescribed amoxicillin-containing products who present with aseptic meningitis after the exclusion of other infectious or disease-related causes. Amoxicillin-associated aseptic meningitis is a very rare but reversible adverse event (AE) that can be managed with drug discontinuation. As such, prompt recognition of this AE could prevent aggressive diagnostic procedures and prolonged treatments, as well as the possibility of recurrent episodes related to subsequent amoxicillin use.

Amoxicillin is a narrow-spectrum beta-lactam antibiotic registered in Singapore since 1998 for the treatment of commonly occurring bacterial infections such as respiratory tract, genitourinary and skin and soft tissue infections. It is available as a single ingredient or in combination with clavulanate, a beta-lactamase inhibitor.

Aseptic meningitis is a condition where the linings of the brain and spinal cord become inflamed without an infectious cause. Drugs such as non-steroidal anti-inflammatory drugs (NSAIDs), intravenous immunoglobulin and antimicrobials, including amoxicillin, have been identified as potential causes of aseptic meningitis. Other causes include neoplasia, autoimmune, or auto-inflammatory systemic diseases (e.g. systemic lupus erythematosus, rheumatoid arthritis) and iatrogenic etiologies such as complications of a lumbar puncture or intrathecal drug adverse effects. The pathogenesis of drug-induced aseptic meningitis remains unclear but an idiosyncratic delayed-type hypersensitivity reaction has been proposed.

Very rare cases of aseptic meningitis associated with the use of amoxicillin-containing products have been published in literature. Patients typically presented with fever and headache which developed a few hours to seven days after amoxicillin exposure. Photophobia, nuchal rigidity, lethargy, myalgia and general malaise were also present in some cases. Notably, most cases demonstrated positive rechallenge, with two to three episodes of amoxicillin-induced aseptic meningitis. Typical cerebrospinal fluid (CSF) findings consisted of pleocytosis (lymphocytic or neutrophilic), which in some cases was accompanied by elevated protein and usually normal glucose levels (unlike low CSF glucose in bacterial meningitis). CSF cultures were consistently negative.

The diagnosis of amoxicillin-induced aseptic meningitis is usually based on a temporal relationship between drug intake and symptom onset, CSF pleocytosis, negative microbiological tests, and rapid resolution, usually within a few days, after drug discontinuation. As it is a diagnosis of exclusion, a thorough drug history can help support a diagnosis of amoxicillin-associated aseptic meningitis after infectious and disease-related (mainly neoplasms and autoimmune disorders) causes of aseptic meningitis have been ruled out.

In 2021, Health Canada reviewed the potential risk of aseptic meningitis in patients treated with amoxicillin-containing products and concluded that there might be a link between amoxicillin-containing products and the risk of aseptic meningitis. Their review took into consideration domestic and international cases of aseptic meningitis associated with amoxicillin use as well as a study of international cases reported to

the World Health Organisation (WHO) database, which supported a link between the risk of aseptic meningitis and the use of amoxicillin.

To date, HSA has received one report of aseptic meningitis that was possibly associated with the use of amoxicillin/clavulanic acid.

Currently, aseptic meningitis is a documented AE in the package inserts (PIs) of some amoxicillin-containing products. HSA is working with the product registrants of the remaining products to harmonise this safety information across the local PIs of all amoxicillin-containing products.

In Hong Kong, there are 169 registered pharmaceutical products for human use containing amoxicillin and are prescription-only medicines. As of the end of May 2022, the Department of Health (DH) had received 26 cases of adverse drug reaction related to amoxicillin, but these cases were not related to aseptic meningitis. Related news was previously issued by Health Canada and was reported in Drug News Issue No. 146. The DH issued letters to inform local healthcare professionals to draw their attention on 13 December 2021. The DH will keep vigilant on any further safety updates from other overseas drug regulatory authorities.

The United Kingdom: Denosumab 60mg (Prolia): should not be used in patients under 18 years due to the risk of serious hypercalcaemia

On 17 May 2022, Medicines and Healthcare products Regulatory Agency (MHRA) announced that serious and life-threatening hypercalcaemia has been reported with denosumab 60mg (Prolia) in children and adolescents in clinical trials for osteogenesis imperfecta and during off-label use. Denosumab 60mg (Prolia) is authorised for use in adults with osteoporosis and other bone loss conditions, it should not be used in children and adolescents younger than 18 years.

Cases of serious and life-threatening hypercalcaemia requiring hospitalisation and complicated by acute renal injury have been reported in children and adolescents younger than 18 years receiving 60mg denosumab in clinical trials. These clinical trials were investigating treatment with denosumab in patients younger than 18 years with osteogenesis imperfecta. Osteogenesis imperfecta is a group of rare inherited conditions that cause very fragile bones.

Worldwide, MHRA is also aware of 20 suspected adverse event reports of hypercalcaemia reported up to 26 August 2021, during off-label treatment with Prolia in children and adolescents younger than 18 years. Reports included cases in paediatric patients with osteogenesis imperfecta, as well as in those with various other conditions. There were also a small number of reports of hypercalcaemia in patients younger than 18 years after stopping treatment (rebound hypercalcaemia).

Symptoms of hypercalcaemia include excessive thirst, excessive urination, drowsiness, confusion, loss of concentration, feeling or being sick, constipation, and muscle weakness. Severe hypercalcaemia can cause serious kidney problems (acute renal injury), coma, heart rhythm abnormalities and cardiac arrest.

A recent European review assessed these cases of severe hypercalcaemia and recommended stronger warnings against use of Prolia in children and adolescents younger than 18 years. MHRA has considered this review together with the safety data and agrees that the product information should be updated. The Summary of Product Characteristics for Prolia has been updated to advise that denosumab 60mg should not be used in children and adolescents younger than 18 years because of safety concerns about serious hypercalcaemia. There are also existing warnings that inhibition of RANK/RANK ligand (RANKL) in animal studies may be associated with inhibition of bone growth and lack of tooth eruption.

Advice for healthcare professionals:

- Denosumab 60mg (Prolia) is authorised for use only in adults (aged 18 years and older) for treatment of osteoporosis and other bone loss conditions.
- Serious and life-threatening hypercalcaemia has been reported with denosumab 60mg use in children and adolescents in clinical trials and during off-label use.
- Hypercalcaemia cases occurred during treatment or in the weeks to months after the last dose.
- Denosumab 60mg (Prolia) should not be used in children and adolescents younger than 18 years.

In Hong Kong, Prolia Solution For Injection In Pre-filled Syringe 60mg/ml (USA) (HK-60588)

and Prolia Solution For Injection In Pre-filled Syringe 60mg/ml (The Netherlands) (HK-60589) are registered by Amgen Hong Kong Limited. Both products are prescription-only medicines. As of the end of May 2022, the Department of Health (DH) had received 59 cases of adverse drug reaction related to denosumab, but these cases were not related to hypercalcaemia.

Related news on hypercalcaemia after cessation of treatment with denosumab in paediatric patients and monitoring in those patients with growing skeletons was previously issued by Singapore Health Sciences Authority, and was reported in Drug News Issue No. 70. In light of the above MHRA's announcement, the DH issued letters to inform local healthcare professionals to draw their attention on 18 May 2022 and the matter will be discussed by the Registration Committee of the Pharmacy and Poisons Board.

European Union: Synchron Research Service: Suspension of medicines over flawed studies

On 20 May 2022, European Medicines Agency (EMA) announced that its human medicines committee, Committee for Medicinal Products for Human Use (CHMP), has recommended the suspension of the marketing authorisations of several generic medicines tested by Synchron Research Services, a contract research organisation (CRO) located in Ahmedabad, India.

The recommendation comes after irregularities were found in how the CRO carried out bioequivalence studies, which raised serious concerns about the company's quality management system and the reliability of data from that site. Bioequivalence studies are conducted to show that a generic medicine releases the same amount of active substance in the body as the reference medicine.

The CHMP looked at all medicines tested by Synchron Research Services on behalf of European Union (EU) companies and found that for the majority (around 100 medicines) no adequate bioequivalence data were available from other sources. The Committee recommended that these medicines be suspended. To lift the suspension, companies relying on data from Synchron Research Services must provide alternative data demonstrating bioequivalence. For a small number of authorised generic medicines (around 20), adequate bioequivalence data were available from other sources, and these medicines are allowed to remain on the EU market.

With just a couple of exceptions for which data from other sources are available, the majority of medicines that were being evaluated for authorisation on the basis of data from Synchron Research Services will not be granted authorisation in the EU.

For details of the affected products, please refer to the website in EMA.

Some of the medicines that have been recommended for suspension may be of critical importance (e.g. due to lack of available alternatives) in a given EU Member State. Therefore national authorities can temporarily postpone the suspension in the interest of patients. Member States should also decide whether recalls of the affected medicines are needed in their territories.

The CHMP's recommendation will now be sent to the European Commission which will issue a legally binding decision in due course.

Information for patients and healthcare professionals:

- Several generic medicines have been suspended from the EU market because the company that tested them is considered unreliable.
- There is no evidence of harm or lack of effectiveness with any of the affected medicines. However, the medicines have been suspended until supporting data from more reliable sources are available.
- Several alternative medicines are available. Patients taking the affected medicines can contact their doctor or pharmacist for more information.
- National authorities in the EU will consider how critical individual medicines are in their countries and make final decisions on whether to suspend or allow them to remain available while new data are generated.

Among the 46 drug ingredients/combinations of drug ingredients recommended for suspension by EMA, submission of bioequivalence data is required for 4 drug ingredients (namely, clobazam, clonazepam, clonidine and gliclazide) for registration of pharmaceutical product in Hong Kong. Currently, there are registered

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pharmaceutical products containing clobazam (3 products), clonazepam (7 products) and gliclazide (17 products). These products are not manufactured by the companies marketing the related products as listed by EMA. In addition, the bioequivalence study of these products submitted for registration were not conducted by Synchron Research Services. There is currently no registered pharmaceutical product containing clonidine. The Department of Health will remain vigilant on any safety update on this matter issued by other overseas drug regulatory authorities.

Canada: Summary Safety Review: Valacyclovir-containing products: Assessing the potential risk of drug reaction with eosinophilia and systemic symptoms (DRESS)

On 24 May 2022, Health Canada announced that it reviewed the potential risk of drug reaction with eosinophilia and systemic symptoms (DRESS) with the use of valacyclovir-containing products. This safety review was triggered by updates made by the European Medicines Agency to the product safety information for valacyclovir-containing products to include the risk of DRESS.

DRESS is a rare, but serious, and potentially life-threatening drug reaction that includes fever, severe skin rash or peeling of the skin over large areas of the body, swollen face and high white blood cell count, affecting one or more organs. The symptoms of DRESS typically appear within 2 weeks to 2 months after starting a medication. DRESS is also known as drug rash with eosinophilia and systemic symptoms, drug induced hypersensitivity syndrome or DRESS syndrome.

Health Canada reviewed information provided by the manufacturer of the brand name product, and from searches of the Canada Vigilance database and the published literature. Health Canada reviewed 115 cases (3 Canadian, 112 international) of DRESS in patients taking valacyclovir. Of the 115 cases, 26 (international) met the criteria for further assessment to determine if there was a link between the use of valacyclovir and DRESS. Of the 26 case reports, 4 cases, including 3 published in the scientific literature, were found to be probably linked to the use of valacyclovir. Twenty-one cases, including 1 death, were found to be possibly linked, and 1 case was unlikely to be linked to the use of valacyclovir. In 25 of the 26 cases, patients were also taking other medications known to cause DRESS.

Health Canada's review of the available information concluded that there may be a link between the use of valacyclovir-containing products and the potential risk of DRESS. Health Canada will work with the manufacturers to update the Canadian product safety information for valacyclovir-containing products to include the risk of DRESS.

In Hong Kong, there are 12 registered pharmaceutical products containing valacyclovir. All products are prescription-only medicines. As of the end of May 2022, the Department of Health (DH) had not received any case of adverse drug reaction related to valacyclovir. In light of the above Health Canada's announcement, the DH issued letters to inform local healthcare professionals to draw their attention on 25 May 2022 and the matter will be discussed by the Registration Committee of the Pharmacy and Poisons Board.

Drug Recall

Batch recall of Valsartan HCT Stada Tablets 80mg/12.5mg

On 31 May 2022, the Department of Health (DH) endorsed a licensed drug wholesaler, Hong Kong Medical Supplies Ltd (HKMS), to recall one batch (batch number: 12E2YD) of Valsartan HCT Stada Tablets 80mg/12.5mg (Hong Kong Registration number HK-62705) from the market because the product's manufacturer address of the concerned batch does not match with the registered one.

The DH received notification from HKMS that they were informed by the overseas manufacturer that the address of the manufacturing site was different from the registered one, and this renders the product unregistered. Since supply of unregistered pharmaceutical product contravenes the Pharmacy and Poisons Regulations (Cap. 138A), HKMS voluntarily recalls the concerned batch of product from the market. DH's investigation is continuing.

The above product, containing valsartan and hydrochlorothiazide, is a prescription medicine used in the management of hypertension. According to HKMS, the concerned batch of

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product has been supplied to private doctors and pharmacies.

As of the end of May 2022, the DH had not received any adverse drug reaction report related to the affected batch of the above product. A notice was posted on the Drug Office website on 31 May 2022 to alert the public of the product recall. The DH will closely monitor the recall.

Batch recall of Chlor Oph Eye Drop 0.5%

On 31 May 2022, the Department of Health (DH) endorsed a licensed drug wholesaler, Health Alliance International Co Ltd (Health Alliance), to recall one batch (batch number: 22981) of Chlor Oph Eye Drop 0.5% (Hong Kong Registration number HK-45255) from the market due to potential quality issue.

The DH received notification from Health Alliance indicating that they were informed by the overseas manufacturer of potential quality issue of the active ingredient. According to Health Alliance, no quality issue is so far revealed in the locally distributed eye drops. As a precautionary measure, Health Alliance is voluntarily recalling the product of concerned batch from the market.

The above product, containing chloramphenicol, is an antibiotic used for the treatment of superficial eye infections. According to Health Alliance, the above batch of product has been supplied to private doctors and pharmacies.

As of the end of May 2022, the DH had not received any adverse drug reaction report related to the affected batch of the above product. A notice was posted on the Drug Office website on 31 May 2022 to alert the public of the product recall. The DH will closely monitor the recall.

Drug Incident

Public urged not to buy or consume oral product containing undeclared controlled ingredients

On 11 May 2022, the Department of Health (DH) appealed to the public not to buy or consume an oral product (The product has no English name, please refer to the photo in the press release for details) as it was found to contain undeclared controlled drug ingredients.

During the DH's market surveillance, a sample of the product, which comprises a bottle of capsules and a bottle of tablets, was purchased from a licensed pharmacy in Tuen Mun for analysis. Test results from the Government Laboratory revealed that the capsules and tablets contained indomethacin and dexamethasone respectively. Both ingredients are Part 1 poisons under the Pharmacy and Poisons Ordinance (Cap 138). The product is also suspected to be an unregistered pharmaceutical product.

The DH conducted an operation against the above pharmacy on 11 May 2022, during which a 26-year -old man was arrested by the Police for suspected illegal sale of Part 1 poisons and unregistered pharmaceutical product. The DH's investigation is continuing.

Indomethacin is a non-steroidal anti-inflammatory drug used to relieve pain and inflammation. Its side effects include gastrointestinal discomfort, nausea and peptic ulcer. Dexamethasone is a steroid drug used for treating inflammation. Its side effects include moon face, high blood pressure, high blood sugar, muscle atrophy, adrenal insufficiency and osteoporosis. Indomethacin and dexamethasone are prescription medicines which should only be used under the advice of a medical doctor and can only be supplied at pharmacies under the supervision of a registered pharmacist upon a doctor's prescription.

The DH referred the case to other enforcement agencies to follow up.

Upon completion of its investigation, the DH will seek advice from the Department of Justice on prosecution matters and will also refer the relevant case to the Pharmacy and Poisons Board of Hong Kong for consideration of possible disciplinary action.

A press release was posted on the Drug Office website on 11 May 2022 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 $50,000 fine and one year's imprisonment for each offence.

Under the Import and Export Ordinance (Cap. 60), pharmaceutical products must be imported or exported under and in accordance with an import or export licence issued under the Import and Export Ordinance. Illegal import or export of pharmaceutical products are offences under the Import and Export Ordinance (Cap. 60) and the maximum penalty is a fine of $500,000 and 2 years' imprisonment.

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: Adverse Drug Reaction and Adverse Event Following Immunization Unit,
Drug Office, Department of Health,
Room 1856, 18/F, Wu Chung House,
213 Queen's Road East,
Wanchai, Hong Kong

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