Drug News
藥 物 情 報

Issue Number 107

This is a monthly digest of local and overseas drug safety news released by the Drug Office of the Department of Health in September 2018 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

The United States: FDA Drug Safety Communication: FDA to evaluate potential risk of neural tube birth defects with HIV medicine dolutegravir (Juluca, Tivicay, Triumeq): Update

On 6 September 2018, the United States (US) Food and Drug Administration (FDA) announced that, as an update in September 2018, the information regarding serious cases of neural tube birth defects involving the brain, spine, and spinal cord reported in babies born to women treated with dolutegravir used to treat human immunodeficiency virus (HIV) has been addressed in product labeling.

In Hong Kong, there are 2 registered pharmaceutical products containing dolutegravir, namely Tivicay Tablets 50mg (HK-63516) and Triumeq Tablets (HK-64012). Both products are registered by GlaxoSmithKline Limited, and are prescription-only medicines. As on 5 October 2018, the Department of Health (DH) has received 3 cases of adverse drug reaction related to dolutegravir, but these cases are not related to birth defects.

Related news was previously issued by various overseas drug regulatory authorities, and was reported in the Drug News Issue No. 103. DH issued letters to inform local healthcare professionals of the above safety information on 21 May 2018. In light of the above FDA's announcement, the matter will be discussed by the Registration Committee of the Pharmacy and Poisons Board. The DH will maintain vigilant on any further update from these health authorities for consideration of any action deemed necessary.

Canada: Summary Safety Review - Beta-lactam antibiotics - Assessing the potential risk of severe skin side effects

On 10 September 2018, Health Canada announced that it reviewed the risk of Severe Cutaneous Adverse Reactions (SCAR) with beta-lactam antibiotics because of information submitted by a manufacturer that suggested a potential risk of SCAR with amoxicillin-clavulanic acid. Since the risk of SCAR is included in the product information for some beta-lactam antibiotics, Health Canada decided to review all beta-lactam antibiotics, focusing on products that do not already include SCAR in their product information. These reactions include Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), acute generalized exanthematous pustulosis (AGEP) and drug reaction with eosinophilia and systemic symptoms complex (DRESS).

At the time of the review, Health Canada had received 45 Canadianc reports of SCAR related to beta-lactam antibiotics use. Of these reports, 26 were further assessed as they met the criteria set for

this review. Of these 26 reports, 19 were found to have a possible link between the use of beta-lactam antibiotics and SCAR, 4 unlikely to have a link and 3 could not be assessed due to lack of information. A search in the World Health Organization's Adverse Drug Reaction Database found 8855 reports of SCAR in patients treated with beta-lactam antibiotics. Health Canada's review found that there was more frequent reporting of SCAR for the majority of beta-lactam antibiotics than expected in the general population. This safety review also examined the medical and scientific literature. There were 9 published studies and 79 reported cases of SCAR for beta-lactam antibiotics. Health Canada's review of the published studies and cases supported a possible link between SCAR and beta-lactam antibiotics use.

Health Canada's review found a possible link between the use of beta-lactam antibiotics and the risk of SCAR. Health Canada will be working with manufacturers to update the product safety information of beta-lactam antibiotics (that do not already include SCAR) to inform healthcare professionals and patients about this potential risk.

In Hong Kong, as on 5 October 2018, there are 664 registered pharmaceutical products which are beta-lactam antibiotics, including penicillins, cephalosporins and related drugs. All products are prescription-only medicines. As on 5 October 2018, DH has received 32 cases of adverse drug reaction related to beta-lactam antibiotics, of which one case is related to Stevens-Johnson syndrome. In light of the above Health Canada's announcement, DH issued letters to inform local healthcare professionals to draw their attention on 11 September 2018, and the matter will be discussed by the Registration Committee of the Pharmacy and Poisons Board.

The United Kingdom: Valproate Pregnancy Prevention Programme: Actions required now from GPs, specialists, and dispensers

On 25 September 2018, Medicines and Healthcare products Regulatory Agency (MHRA) announced that valproate medicines must not be used in women of childbearing potential unless the Pregnancy Prevention Programme is in place; and it reminded the healthcare professionals, such as general practitioners (GPs), specialists and dispensers to start action for the programme.

The healthcare professionals are reminded for the following:

General Practitioners

- Identify and recall all women and girls on valproate who may be of childbearing potential
- Provide the Patient Guide to the patients (or her parents or responsible person as necessary); and check that they have been reviewed by a specialist in the last year (i.e.: they have an in-date Risk Acknowledgement Form) and are on highly effective contraception

Specialists

- Book in review appointments at least annually with women and girls under the Pregnancy Prevention Programme and re-evaluate treatment as necessary
- Explain clearly the conditions as outlined in the supporting materials
- Complete and sign with the patient or their responsible person the Risk Acknowledgement Form-copies of the form must be given to the patient or responsible person and sent to their GP

Dispensers

- Valproate medicines must always be dispensed with the accompanying patient information leaflet
- Dispense whole packs whenever possible, and ensure there is a warning label either on the carton or added via a sticker
- Discuss risks in pregnancy with female patients each time you dispense valproate medicines and ensure they have the Patient Guide and have seen their GP or specialist to

discuss their treatment and the need for contraception
- Ensure new packs of valproate information materials are placed in a designated place accessible to all dispensing staff and dispose of any old materials related to valproate medicines

The MHRA states that packs of information materials to support informing women on valproate of the risks in pregnancy and the need to be enrolled in the Pregnancy Prevention Programme have already been sent to prescribers, dispensers, and healthcare professionals. As stated in the risk minimisation materials, the requirement for a Pregnancy Prevention Programme is applicable to all premenopausal female patients unless the prescriber considers that there are compelling reasons to indicate that there is no risk of pregnancy.

In Hong Kong, as on 5 October 2018, there are 11 registered pharmaceutical products containing valproic acid and/or valproate, and all products are prescription-only medicines. As on 5 October 2018, DH has received 9 cases of adverse drug reaction related to valproic acid or valproate, but these cases are not related to adverse effects on new-born babies whose mothers took valproate for their medical conditions.

Related news on the recent review of valproate was previously issued by various overseas drug regulatory authorities, and was reported in the Drug News Issue No. 90 and 100. DH issued letters to local healthcare professionals to draw their attention to the European Medicines Agency (EMA) recent review on 12 February 2018.

In December 2014, the Registration Committee of the Pharmacy and Poisons Board discussed the findings of an EMA previous review on the risk of valproate products in pregnancy and had decided that warnings and precautions on the risk of pregnancy should be included in valporate products. In light of the new reviews from overseas drug regulatory authorities and the above MHRA's announcement, the matter will be discussed by the Registration Committee of the Pharmacy and Poisons Board. DH will stay vigilant on any relevant safety update of the drug issued by other overseas drug regulatory authorities.

The United Kingdom: Nusinersen (Spinraza ▼) : Reports of communicating hydrocephalus; discuss symptoms with patients and carers and investigate urgently

On 25 September 2018, MHRA advised patients and their caregivers to seek urgent medical attention if any signs or symptoms of the communicating hydrocephalus develop during the nusinersen therapy for spinal muscular atrophy. Patients with the communicating hydrocephalus may require treatment with a cerebrospinal fluid (CSF) shunt.

Nusinersen (Spinraza ▼) is an antisense oligonucleotide indicated for the treatment of 5q spinal muscular atrophy that was first authorised in December 2016. Nusinersen is given intrathecally by lumbar puncture as 4 loading doses on days 0, 14, 28, and 63 of therapy, followed by maintenance doses every 4 months.

Worldwide, 5 cases of communicating hydrocephalus have been reported up to 6 July 2018 during routine clinical use of nusinersen. Of the 5 cases, 4 were children with spinal muscular atrophy type 1 who presented with signs of hydrocephalus after receiving 2 to 4 loading doses and one was an adult with scoliosis. Three of the children required CSF drainage procedures and continued nusinersen treatment (2 had ventriculoperitoneal shunts). One child did not require a CSF shunt and is being monitored after nusinersen was discontinued.

There is no known association between spinal muscular atrophy and communicating hydrocephalus and investigations did not reveal an underlying cause such as intracranial haemorrhage or infection.

Worldwide, up to 30 September 2017, approximately 1,437 patients have received nusinersen in routine clinical practice (439 patient-years). There were not any reports of hydrocephalus associated with nusinersen treatment in the United Kingdom, although usage is currently very limited.

Healthcare professionals should discuss with patients, and their caregivers if necessary, the risk

of hydrocephalus and advise them to seek urgent medical attention if any signs or symptoms of hydrocephalus develop including persistent vomiting or headache, seizures, decreased consciousness, or a rapid increase in head size in children.

Hydrocephalus should be considered in any patient with suggestive clinical features and confirmed cases should be referred urgently to a neurosurgeon for advice on further management.

The effectiveness and safety of nusinersen in patients with CSF shunts has not been determined. If nusinersen is continued, prescribers should continue to monitor the response to therapy. There are no data on the complication rate of CSF shunts with continued nusinersen treatment and the elimination rate of nusinersen from the central nervous system following CSF shunt insertion has not been determined. If a CSF shunt is required, patients and their carers should be informed that the risks and benefits of nusinersen in patients with CSF shunts are not known.

The healthcare professionals are advised on the following:

- Communicating hydrocephalus has been rarely reported during treatment with nusinersen; most cases developed after 2 to 4 loading doses
- Discuss the risk of the communicating hydrocephalus and its clinical features with patients and their caregivers; and advise them to seek urgent medical attention if any possible symptoms or signs develop including: persistent vomiting or headache, decreased consciousness, or a rapid increase in head size in children
- Consider any patient with suggestive symptoms and signs of the communicating hydrocephalus in the differential diagnosis; and investigate them urgently
- Refer patients with hydrocephalus to a neurosurgeon as soon as possible as they may require treatment with a CSF shunt
- If a CSF shunt is considered necessary, prescribers should inform patients and their carers that the benefits and risks of continued nusinersen treatment in patients with CSF shunts are not known
- Report any suspected adverse drug reactions to nusinersen on a Yellow Card, including hydrocephalus or any problems after insertion of a CSF shunt

In the United Kingdom, the risk of hydrocephalus has been added to the product information for nusinersen and prescribing clinicians were informed of this risk by letter in August 2018. As a new medicine, the benefits and risks of this medicine are being reviewed regularly, including any further data about the risk of hydrocephalus and the effectiveness and safety of nusinersen in patients with CSF shunts. The marketing authorisation holder is also conducting additional studies into the safety of nusinersen.

In Hong Kong, Spinraza Solution for Injection 12mg/5ml (HK-65896) is a pharmaceutical product containing nusinersen which is registered by Zuellig Pharma Ltd (Zuellig); and is a prescription-only medicine. As on 5 October 2018, DH has not received any cases of adverse drug reaction with nusinersen. As confirmed with Zuellig, it will update the package insert of the product to include the safety information on hydrocephalus. In light of the MHRA's announcement, DH issued letters to inform local healthcare professionals on hydrocephalus on 26 September 2018. The DH will keep vigilant on any further update from the MHRA and other overseas drug regulatory authorities.

The United States: FDA places Zhejiang Huahai Pharmaceuticals on import alert

On 28 September 2018, the US FDA placed Zhejiang Huahai Pharmaceuticals (ZHP) on import alert, to protect US patients while the active pharmaceutical ingredient (API) manufacturer fully determines how impurities were introduced into its API and remediates its quality systems. The import alert stops all API made by ZHP and finished drug products made using ZHP's API from legally entering the United States. FDA's action follows a recent inspection at ZHP's facility.

FDA reminded manufacturers that it is their responsibility to develop and use suitable methods

to detect impurities, including when they make changes to their manufacturing processes. If a manufacturer detects new or higher levels of impurities, they should fully evaluate the impurities and take action to ensure the product is safe for patients.

In Hong Kong, as on 5 October 2018, there are 253 registered pharmaceutical products containing valsartan (83 products), candesartan (19 products), irbesartan (64 products), losartan (70 products) and olmesartan (17 products). All products are prescription-only medicines.

Regarding impurities in valsartan, a public announcement was issued on 6 July 2018, and DH issued letters to inform local healthcare professionals on 6 July 2018, 9 July 2018, 25 July 2018 and 3 August 2018. Related news for the detection of impurities in sartan-containing products was also previously issued by various overseas drug regulatory authorities, and was reported in the Drug News Issue No. 105 and 106.

In summary, there are four manufacturers, namely Zhejiang Huahai, Zhejiang Tianyu and Zhuhai Rundu in China and Hetero Labs Limited in India, reported to have detection of trace amounts of N-nitrosodimethylamine (NDMA) in the valsartan API by various overseas drug regulatory authorities. The DH contacted the certificate holders of all registered valsartan products to follow up on the local impact regarding valsartan API produced by the above mentioned manufacturers.

For API produced by Zhejiang Huahai, there are 5 affected products (HK-61786, HK-61787, HK-61784, HK-61785 and HK-60794) marketed in Hong Kong. The DH instructed the certificate holders to recall all the products from the market as a precautionary measure on 6 July 2018, and the DH noted that all the recalls have been completed.

For API produced by Zhejiang Tianyu, amongst the registered pharmaceutical products containing valsartan, there is only one product namely Retoni Tablets 80mg (HK-65604) registered by Swiss Pharmaceutical Co Limited (Swiss Pharmaceutical) which has used API produced by Zhejiang Tianyu and is available in the local market. As confirmed with Swiss Pharmaceutical, the API was tested by the Taiwan Food and Drug Administration (TFDA) and the company has not received any notice from the TFDA for NDMA contamination. The DH collected samples of Retoni tablets for analysis and no NDMA was detected.

For API produced by Zhuhai Rundu and Hetero Labs Limited, the certificate holders confirmed that the valsartan products available in local market are not manufactured using API produced by Zhuhai Rundu or Hetero Labs Limited.

Regarding the announcements issued by various overseas drug regulatory authorities on the detection of the second impurity of N-nitrosodiethylamine (NDEA) in the valsartan API produced by Zhejiang Huahai, there should be no local impact as all valsartan products manufactured using API produced by Zhejiang Huahai have been recalled from the market.

Regarding the EMA's announcement on the detection of NDEA in losartan in the API produced by Hetero Labs Limited, as on 5 October 2018, the DH has contacted the certificate holders of all registered candesartan, irbesartan, losartan and olmesartan products and will continue to follow up on the impact of NDEA impurities on the products available in the local market.

As on 5 October 2018, DH has received 14 cases of adverse drug reaction related to valsartan,

candesartan, irbesartan, losartan and olmesartan. None of them are concluded to be related to the presence of NDMA and/or NDEA. The DH will keep vigilant on any further updates on the matter issued by overseas drug regulatory authorities.

Patients who are taking the above products should not stop taking the medicines, but should seek advice from their healthcare professionals as soon as possible for proper arrangement.

The DH has provided update information at Drug Office's website (www.drugoffice.gov.hk) and will remain vigilant on any safety update related to the impurities NDMA and NDEA in sartan-containing (candesartan, irbesartan, losartan, olmesartan and valsartan) products.

Drug Recall

Batch recall of Ethosuximide Capsules USP 250mg

On 3 September 2018, DH endorsed three licensed drug wholesalers, namely Hua Tai Pharmaceuticals Co. Ltd. (Hua Tai), Trackcircle.com Limited (Trackcircle) and Vantone Medical Supplies Co. Ltd. (Vantone) to recall two batches of Ethosuximide Capsules USP 250mg (batch numbers: 1165280100 and 1165280101) from the market because of a potential quality issue.

The DH received notification from Hua Tai that the distributor of the above product in the United States had informed Hua Tai to recall two batches (1165280100 and 1165280101) of the product from the market due to out of specification results on impurity of the product. According to Hua Tai, 35 bottles of the affected batches were imported and supplied to one public hospital and one private doctor for the treatment of particular patients.

Besides, according to the DH import records, two other licensed drug wholesalers had imported the affected batches into Hong Kong for the treatment of particular patients, including Trackcircle imported 10 bottles of one affected batch (1165280100) and supplied to another public hospital, and Vantone imported 2 bottles of another affected batch (1165280101) and supplied to a private hospital.

Hua Tai, Trackcircle and Vantone had informed the respective public and private hospitals, and the private doctor about the recall.

The above Ethosuximide Capsules USP 250mg is not a registered pharmaceutical product in Hong Kong and is an antiepileptic drug for the treatment of seizures. As on 5 October 2018, the recall had already been completed.

A notice was posted on the website of Drug Office on 3 September 2018 to alert the public of the product recall.

Batch recall of Ozurdex Intravitreal Implant 700mcg (HK-60336)

On 28 September 2018, DH endorsed a licensed drug wholesaler Allergan Hong Kong Limited (Allergan) to recall two batches (E79233 and E80405) of Ozurdex Intravitreal Implant 700mcg (HK-60336) from the market because of potential quality issue.

The DH received notification from Allergan that during routine testing by the manufacturer in Ireland, a silicone particle from the silicone sleeve component on the needle of the applicator was generated upon actuation of the Ozurdex unit which would give rise to the potential for the silicone particle to be injected during administration of the Ozurdex implant into the eye. Allegran recalls the affected batches as a precautionary measure.

The above Ozurdex product, containing dexamethasone, is a prescription-only medicine used to treat macular disease. According to Allergan, the product has been supplied to Hospital Authority, private hospitals, private doctors and re-exported to Macao.

Drug Recall

Allergan has issued letter to healthcare professionals and set up a hotline (2895 9668) to answer enquiries on the above recall.

As on 5 October 2018, DH has not received any adverse reaction reports in connection with the above batches of the product.

Members of the public should consult healthcare professionals if in doubt or feeling unwell after using the product. A notice was posted on the website of Drug Office on 28 September 2018 to alert the public of the product recall.

Drug Incident

DH raids retail shops for suspected illegal sale and possession of unregistered pharmaceutical product

On 20 September 2018, DH and the Police in a joint operation raided two retail shops in Sheung Shui and Yuen Long for suspected illegal sale and possession of an unregistered pharmaceutical product. Three people were arrested during the operation.

During market surveillance, the DH found that the two retail shops had been selling an unregistered pharmaceutical product, which was labeled in Japanese as containing dexamethasone, a Part 1 poison under the Pharmacy and Poisons Ordinance (PPO) (Cap 138).

Dexamethasone is a steroidal substance for treating inflammation. Inappropriate or excessive application of steroids could cause skin problems. Products containing dexamethasone are prescription medicines and should be used under the advice of medical practitioners.

A man aged 20 and two women aged 24 and 50 were arrested by the Police for suspected illegal sale and possession of Part 1 poison and unregistered pharmaceutical product in the operation.

A press statement alerting the public of the incident was issued on 20 September 2018.

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.

Under the Import and Export Ordinance (Cap. 60), pharmaceutical products must be imported or exported under and in accordnance 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: ***Pharmacovigilance Unit,***
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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.