Drug News
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Issue Number 62

This is a monthly digest of local and overseas drug safety news released by the Drug Office of the Department of Health in December 2014 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 Mainland: Alert on Adefovir dipivoxil and the associated risks of hypophosphatemia and osteomalacia

On 10 December 2014, the China Food and Drug Administration (CFDA) of the Mainland alerted on the risks of hypophosphatemia and osteomalacia associated with adefovir dipivoxil.

Adefovir dipivoxil was first marketed in China in 2005 and is available in two dosage forms, namely tablets and capsules. It is clinically used in the treatment of chronic hepatitis B in adults with compensated liver disease with evidence of active viral replication, accompanied with persistently raised serum aminotransferase (ALT or AST) concentrations or histological evidence of active liver disease.

The analysis from the National Centre for Adverse Drug Reaction Monitoring database suggests that long-term use of adefovir dipivoxil can cause hypophosphatemia and osteomalacia. Osteomalacia mainly involves unmineralised osteoid proliferation and bone softening which may produce bone pain, bone deformities, fractures and a series of clinical symptoms and signs.

The National Centre for Adverse Drug Reaction Monitoring database received 21 adverse drug reaction reports on osteomalacia caused by adefovir dipivoxil. Apart from osteomalacia, there were reports on renal tubular acidosis, renal tubulopathy, Fanconi syndrome, fractures, etc. and all were accompanied with hypophosphatemia. Osteomalacia caused by adefovir dipivoxil has long occurrence cycle, progresses slowly, and mostly occurs after 3 years' drug use. Hypophosphataemia may also occur at early stage. Patients can have a good prognosis if adefovir dipivoxil is withdrawn or other measures such as symptomatic treatment are taken.

The CFDA recommends that:

- clinicians should fully understand and timely identify the adverse drug reactions of adefovir dipivoxil. They should promptly discontinue the drug or take other measures such as symptomatic treatment if hypophosphatemia and osteomalacia occur. They should also carry out routine monitoring of renal function and serum phosphorus on patients who are treated with adefovir dipivoxil,
- the relevant manufacturers should revise the relevant contents of the product package insert, enhance the promotion on adverse drug reaction monitoring and clinical drug safety, and ensure product safety information can be timely conveyed to patients and physicians in order to reduce and prevent the occurrence of serious adverse drug reactions.

In Hong Kong, there are two registered pharmaceutical products containing adefovir dipivoxil and they are prescription only medicines. The package inserts of the products have included the related safety information on the risks of hypophosphatemia and osteomalacia. So far, the Department of Health (DH) has not received any adverse drug reaction report in relation to the drug. The DH keeps vigilance against any safety updates of the drug.

US: Ziprasidone: Rare but potentially fatal skin reactions

On 11 December 2014, the Food and Drug Administration (FDA) was warning that the antipsychotic drug ziprasidone (marketed in the US

under the brand name, Geodon, and its generics) is associated with a rare but serious skin reaction known as Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS).

DRESS may start as a rash that can spread to all parts of the body. It can include fever, swollen lymph nodes, and inflammation of organs such as the liver, kidney, lungs, heart, or pancreas. DRESS also causes a higher-than-normal number of a particular type of white blood cell called eosinophils in the blood. DRESS can lead to death.

FDA reviewed information from six patients in whom the signs and symptoms of DRESS appeared between 11 and 30 days after ziprasidone treatment was started. None of these patients died. Based on this information, FDA required the manufacturer of Geodon to add a new warning for DRESS to the Warnings and Precautions section of the drug labels for the capsule, oral suspension, and injection formulations. Patients who have a fever with a rash and/or swollen lymph glands should seek urgent medical care. Healthcare professionals should immediately stop treatment with ziprasidone if DRESS is suspected.

In Hong Kong, there are five registered pharmaceutical products containing ziprasidone namely Zeldox for Inj 20mg/ml (with solvent) (HK -51214) and Zeldox Cap 20mg (HK-48922), 40mg (HK-48923), 60mg (HK-48924) and 80mg (HK-48925). All of them are prescription only medicines. So far, the DH has not received any adverse drug reaction report in relation to ziprasidone. In view of the FDA's announcement, a letter to inform local healthcare professionals to draw their attention and urge them to report any adverse drug reactions (ADRs) related to the drug was issued on 12 December 2014. The matter will be discussed in the meeting of the Pharmacy and Poisons (Registration of Pharmaceutical Products and Substances: Certificate of Clinical Trial/ Medicine Test) Committee (the Registration Committee) of the Pharmacy and Poisons Board. The DH remains vigilant on any safety updates of the drug.

Canada: Health products quarantined from two sites in India as Health Canada assesses data integrity concerns

On 23 December 2014, at Health Canada's request, Canadian importers have agreed to quarantine health products from the following two India-based sites due to data integrity concerns:

- Dr. Reddy's Laboratories in Srikakulam, India
- IPCA Laboratories in Pithampur, India

This action comes in light of recent information from a trusted regulatory partner that raises concerns about the reliability of the laboratory data generated at these sites. Health Canada is taking this action as an interim precautionary measure to help mitigate any potential risk. A quarantine means that the Canadian importers have agreed to stop the importation and distribution of products from these two sites. At this time there is no identified risk to health, and Health Canada is not requesting a recall of any of the products.

Health Canada's action applies to active pharmaceutical ingredients (APIs) from Dr. Reddy's Laboratories as well as to finished drug products from a different IPCA Laboratories facility than is currently subject to import restrictions by Health Canada. Health Canada has compiled an initial list of products affected by the quarantine, and is posted on its website. The list will be updated as new information becomes available. To date, none of the affected products have been determined by Health Canada to be medically necessary. Health Canada will continue to work with international partners and Canadian importers to gather and assess information regarding the situation.

In Hong Kong, seven registered pharmaceutical products are involved in the incident, namely Capecitabine Sandoz Tablet 150mg (HK-62913) and Capecitabine Sandoz Tablet 500mg (HK-62914) which are registered by Novartis Pharmaceuticals (HK) Ltd. (Novartis), and PMS-Valsartan Tablets 40mg (HK-62346), 80mg (HK-62378), 160mg (HK-62377), 320mg (HK-62376) and PMS-Domperidone Tab 10mg (HK-47297) which are registered by Trenton-Boma Ltd. (T-Boma). All of the products are prescription only medicines except PMS-Domperidone Tab 10mg which is a pharmacy only medicine. Both Novartis and T-Boma confirmed that the above mentioned products are not manufactured with Active Pharmaceutical Ingredient (API) from the affected sites. The DH keeps vigilant on the updates from Health Canada for consideration of any actions deemed necessary.

Singapore: Risk of hypoglycaemia associated with hydroxychloroquine or chloroquine

On 26 December 2014, the Health Sciences Authority (HSA) would like to inform healthcare professionals about the risk of hypoglycaemia associated with the use of hydroxychloroquine or chloroquine.

Hydroxychloroquine and chloroquine are anti-malarial drugs used for the suppression and treatment of malaria. Hydroxychloroquine is also indicated for the treatment of rheumatoid arthritis, juvenile chronic arthritis, discoid and systemic lupus erythematosus and dermatological conditions caused or aggravated by sunlight.

Hydroxychloroquine is known to potentiate the hypoglycaemic effects of anti-diabetic agents. However, it has been reported in the literature that the risk of hypoglycaemia with hydroxychloroquine was also observed in patients who were not on concomitant hypoglycaemic agents. Two such case reports occur in patients who were prescribed hydroxychloroquine for the treatment of rheumatic diseases. In these case reports, hydroxychloroquine had been identified as the most likely cause of hypoglycaemia in these patients.

There was also a published overseas case report of hypoglycaemia associated with the use of chloroquine. In the report, the patient's blood glucose level repeatedly fell below 36mg/dL despite repeated infusions with dextrose. While the dose and indication for chloroquine use was unknown, a post-mortem toxicological examination found levels of chloroquine to be within the range associated with death from chloroquine poisoning. The authors postulated that the hypoglycaemia was associated with chloroquine poisoning.

Healthcare professionals are advised to be vigilant to possible signs and symptoms of hypoglycaemia in patients prescribed hydroxychloroquine or chloroquine, regardless of concomitant use of hypoglycaemic agents. The HSA is working with the companies to strengthen existing warnings in the local package inserts for hydroxychloroquine- or chloroquine-containing products regarding the additional information on the risk of hypoglycaemia.

In Hong Kong, there are three registered pharmaceutical products containing hydroxychloroquine and one containing chloroquine. All of them are prescription only medicines. In light of the HSA's announcement, a letter to inform local healthcare professionals to draw their attention and urge them to report any ADRs related to the drugs was issued on 29 December 2014. The matter will be discussed in the meeting of the Registration Committee and the DH remains vigilant on safety updates of the two drugs.

Singapore: Risk of thrombotic microangiopathy and nephrotic syndrome associated with the use of interferon beta products

On 26 December 2014, the HSA would like to update healthcare professionals on overseas cases of thrombotic microangiopathy (TMA) and nephrotic syndrome that have been reported with the use of interferon beta products.

Interferon beta products have been registered in Singapore since 1999 and is approved for the treatment of relapsing multiple sclerosis and treatment of patients with a single demyelinating event with an active inflammatory process, who are determined to be at high risk of developing relapsing multiple sclerosis. It is also approved for the treatment of secondary progressive multiple sclerosis with active disease.

Overseas post-marketing cases of TMA, manifested as thrombotic thrombocytopenic purpura (TTP) or haemolytic uraemic syndrome (HUS), including fatal cases, have been reported with the use of interferon beta products. In October 2014, the UK Medicines and Healthcare Products Regulatory Agency (MHRA) issued a drug safety update on a cluster of reports of TMA that occurred with interferon beta. A total of 13 reports of TMA, TTP and/or HUS were received by the MHRA. Clinical features of TMA include thrombocytopenia, new onset hypertension, fever, central nervous system symptoms and impaired renal function.

Overseas cases of nephrotic syndrome with different underlying nephropathies have also been reported in patients treated with interferon beta. Early signs and symptoms of nephrotic syndrome include oedema, proteinuria and impaired renal function, especially in patients at high risk of renal disease.

The Pharmacovigilance Risk Assessment Committee (PRAC) of the European Medicines Agency (EMA) conducted a review on the risk of TMA and nephrotic syndrome associated with the use of interferon beta products in September and May 2013, respectively. In February 2014, PRAC concluded that a causal association between interferon beta products and TMA and nephrotic syndrome could not be ruled out. Consequently, their product labels were updated and a Dear Healthcare Professional Letter was issued to communicate these safety issues to healthcare professionals in the EU.

The local package inserts of interferon beta products in Singapore have been strengthened to include warnings on the risk of these safety concerns. Healthcare professionals are advised to monitor and consider the possibility of TMA and nephrotic syndrome in patients treated with interferon beta products, if signs and symptoms consistent with these diagnoses are identified.

In Hong Kong, there are 11 registered pharmaceutical products containing interferon-beta which are prescription only medicines. Related news has been released by Health Canada and was reported in the Drug Office Issue No. 58. A letter to healthcare professionals to draw their attention and urge them to report any ADRs related to the drug was issued on 25 August 2014. So far, DH has not received any adverse drug reaction report on the drug related to thrombotic microangiopathy and nephrotic syndrome. In light of the latest HSA's announcement, the matter will be discussed in the meeting of the Registration Committee.

Singapore: Update on trend of lymphadenitis and injection-site reactions with the BCG Vaccine SSI

On 26 December 2014, the HSA would like to update healthcare professionals on the trend of lymphadenitis and injection-site reactions associated with the Bacillus Calmette-Guérin (BCG) vaccine SSI®. Since HSA's last update in December 2011 on the increase in local cases of suppurative lymphadenitis, the incidence of lymphadenitis has been on the downtrend.

In Singapore, BCG vaccine is routinely administered to all neonates at birth as part of the National Childhood Immunisation Schedule (NCIS). The BCG vaccine SSI® containing an attenuated strain of Mycobacterium bovis (Danish strain 1331) has been the only BCG vaccine registered in Singapore since June 2003.

An increase in local cases of BCG-associated suppurative lymphadenitis was first observed in 2011, based on the vaccine adverse event (VAE) reports obtained from the active surveillance sentinel site at KK Women's and Children's Hospital (KKH) and spontaneous reporting by healthcare professionals. As of end August 2014, the estimated incidences of suppurative lymphadenitis and non-suppurative lymphadenitis for the 2009 to 2013 vaccinated cohorts ranged from 0.48 to 3.18 per 1,000 vaccinees and 0.10 to 0.79 per 1,000 vaccinees, respectively. Although the upper bound of this estimate was higher than that in the package insert, it still remained within the values that had been reported globally for this brand of vaccine. Following a peak in cases reported in the 2011 vaccinated cohort, the incidences of suppurative and non-suppurative lymphadenitis have since returned to baseline levels.

An investigation into the possible causes behind the higher incidence of suppurative lymphadenitis involving the 2011 vaccinated cohort was conducted by the HSA. Possible causes such as issues related to vaccine quality, vaccine administration practice or techniques and host characteristics were evaluated in detail. The HSA's investigation revealed that the issue may be batch-related as a result of vaccine manufacturing issues, after ruling out vaccine administration-related and host-related factors.

Further investigation conducted by the manufacturer identified the possible cause to be due to a period of manufacturing with a slower growth of the bacilli. One postulation could be that the higher level of bacterial by-products as a result of the slower growth of the bacilli may have triggered lymphadenitis in some patients, although the manufacturer was unable to confirm this. The trending of the incidence of suppurative lymphadenitis of all batches administered from 2009 to 2013 in Singapore appeared to be consistent with the manufacturer's investigation, with lower incidences of suppurative lymphadenitis (0.1–1 per 1,000 vaccinees) reported in batches

Safety Update

manufactured before and after the period of the slower growth issue. Rectifications made by the manufacturer had seen the incidence of suppurative lymphadenitis returning to baseline levels. Further details may be found in the joint publication by the HSA and KKH.

The HSA continues to closely monitor the local VAE reports of BCG-associated lymphadenitis stratified by vaccine batches. Healthcare professionals are encouraged to report the batch number of all vaccines administered according to the NCIS to the National Immunisation Registry, Health Promotion Board, as well as when filing a report of suspected VAE to the HSA. This would help in the identification of any quality-related issues with the suspected vaccine during the investigation of VAEs.

The HSA also wishes to highlight to healthcare professionals that during its close monitoring of all VAEs associated with the BCG vaccine, neonates who were administered this vaccine at the gluteal area appeared to have experienced more injection-site reactions compared to those who were vaccinated at the deltoid area. A total of 13 cases (0.14 per 1,000 vaccinees) of abscess or cellulitis were reported in children who were vaccinated at the gluteal area compared to six cases (0.10 per 1,000 vaccinees) in those vaccinated at the deltoid area for the 2010 to 2013 vaccinated cohorts. This may be contributed in part by the difficulty in caring for the injection site when the vaccine was administered at the gluteal area. Healthcare professionals are advised to take this into consideration during the administration of the BCG vaccine.

In Hong Kong, BCG Vaccine SSI Powder for Inj 0.75mg/ml (HK-44952) is registered by Mekim Ltd. It is manufactured by Statens Serum Institut (Denmark) and is a prescription only medicine. Related news had been released by HSA and was reported in the Drug News Issue No. 26. A letter to inform local healthcare professionals to draw their attention to the issue and urge them to report any ADRs related to the drug was issued on 28 December 2011. BCG vaccine is part of the Hong Kong Childhood Immunisation Programme. Drug Office has received 8 cases of Adverse Event Following Immunisation (AEFI) related to lymphadenitis from 2011 to 2014. The DH continues to remain vigilant on further safety updates related to the vaccine issued by oversea health authorities.

Drug Recall

Recall of Naturally Mega Glucokon Tablets (HK-55131)

On 3 December 2014, the DH instructed a licensed drug wholesaler, Julius Chen & Co. (HK) Ltd. (Julius Chen), to recall all batches of Naturally Mega Glucokon Tablets from the market because the sales label of the product is unapproved. Naturally Mega Glucokon Tablets contains glucosamine and chondroitin which is used as a dietary supplement for joint health. The product can be sold over-the-counter without a prescription.

Upon the DH's investigation into a public enquiry, it was revealed that the sales label of the product in the market did not match with the approved version. As such, the product is considered as unregistered. The quality of product is nonetheless not affected.

According to Julius Chen, the product has been supplied to local pharmacies. The DH will closely monitor the recall. As on 3 December 2014, the DH had not received any adverse reaction report related to the use of the product. A notice was released on the Drug Office's website on the same day to alert the public of the recall.

Recall of one batch Redoxon Double Action Effervescent Tab (HK-49731)

On 4 December 2014, the DH endorsed a licensed drug wholesaler, Bayer Healthcare Ltd. (Bayer), to conduct a voluntary recall of one batch (batch number: CM27292) of Redoxon Double Action Effervescent Tab from the market due to a wrong expiry date printed on the product. Redoxon Double Action Effervescent Tab, containing Vitamin C and Zinc, is an over-the counter medicine used as supplement of Vitamin C and Zinc.

The DH received notification from Bayer that the product's Indonesian manufacturer, PT Bayer, had mistakenly printed the expiry date as November 2016 on the affected batch of product while it

Drug Recall

should be October 2016 instead. The quality of product is nonetheless not affected.

According to Bayer, a total of 5,760 boxes of the affected batch had been imported to Hong Kong in Nov 2014 and they were all supplied to local drug stores. The DH will closely monitor the recall. As on 4 December 2014, the DH had not received any adverse reaction report related to the use of the product. A notice was released on the Drug Office's website on the same day to alert the public of the recall.

Batch recall of Zinc Cream 20g (HK-40872)

On 11 December 2014, the DH endorsed a licensed drug manufacturer, Medipharma Ltd. (Medipharma), to recall two batches (batch numbers: 411749 and 410627) of Zinc Cream 20g from shelves due to a packaging error. Zinc Cream is an over-the-counter medicine used for diaper rash and skin irritation.

The DH was notified by Medipharma of a complaint that two boxes labelled as Zinc Cream 20g were found to contain another Medipharma product, namely Cinotec Cream 0.025% 15g (registration number: HK-19976), inside the box. Preliminary investigation by Medipharma revealed that certain outer boxes for Cinotec Cream 0.025% 15g were wrongly printed with the label of Zinc Cream 20g. These incorrect outer boxes may have been used to pack two batches (batch numbers: 411749 and 410627) of Cinotec Cream 0.025% 15g. As such, products with an outer box labelled as Zinc Cream 20g with the batch numbers 411749 or 410627 are problematic products, as they actually contain an aluminium tube of Cinotec Cream 0.025% 15g bearing the correct label of Cinotec Cream inside the box.

Cinotec Cream, a steroid cream containing fluocinolone, is a prescription medicine for the treatment of eczema and allergic skin disorders. Side-effects of steroid include moon face, high blood pressure, high blood sugar, muscle atrophy, adrenal insufficiency and even osteoporosis.

Medipharma reported that the affected wrongly packed Cinotec Cream 0.025% 15g had been supplied to local pharmacies since October. The DH will closely monitor the recall. As on 11 December 2014, the DH had not received any adverse reaction report related to the use of the product. A notice was released on the Drug Office's website on the same day to alert the public of the recall.

Those who have used the products should consult their healthcare providers if in doubt. They should check the tube label before use.

Drug Incident

Retail stall raided for suspected illegal sale of unregistered pharmaceutical products with undeclared ingredients

On 16 December 2014, a joint operation was conducted by the DH and the Police against a retail stall in Tin Shui Wai resulting in the arrest of a man aged 27 for suspected illegal sale and possession of unregistered pharmaceutical products that contain undeclared Part I poisons and antibiotics.

The DH was previously notified by the Hospital Authority of a 37-year-old male patient who was found to have deranged liver function after using a cream (no English name) purchased from a retail stall. The patient attended Tsueng Kwan O Hospital but no admission was required. He has been in stable condition all along.

In the DH's investigation of the case, the concerned product together with other similar products found in a retail stall was purchased for analysis. Analytical results from the Government Laboratory revealed that two of the products, including the concerned product (no English names), contain metronidazole, miconazole, erythromycin, chloramphenicol, chlorpheniramine and salicylic acid. In addition, the concerned product also contains griseofulvin, methyl salicylate and trace amount of dexamethasone and clobetasol.

Metronidazole, miconazole, dexamethasone and clobetasol are part I poisons whereas erythromycin, chloramphenicol and griseofulvin are antibiotics. Products containing dexamethasone, clobetasol, erythromycin, chloramphenicol and griseofulvin are prescription medicines which should only be used under the advice of a medical doctor and could only be supplied at pharmacies under the supervision of a registered pharmacist upon doctor's prescription.

Erythromycin, chloramphenicol, metronidazole are

used topically for treatment of various microbial infection of skin, side effects include pruritus and skin rash. Hepatotoxicity cases have also been reported. Symptoms of hepatotoxicity include nausea, vomiting, loss of appetite and yellow skin. Miconazole and griseofulvin are used for treatment of fungal infection of skin, side effects include local irritation and sensitivity reactions. Dexamethasone and clobetasol are steroids, side effects include moon face, high blood pressure, high blood sugar, muscle atrophy, adrenal insufficiency and even osteoporosis.

Methyl salicylate is used topically for the relief of musculoskeletal pain, side effects include skin irritation. Salicylic acid is applied topically in the treatment of skin conditions such as acne, side effects include dermatitis, and less commonly skin ulceration. Chlorpheniramine is an antihistamine for the treatment of allergic reaction and its side effects include blurred vision and drowsiness.

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 I poisons should be sold at registered pharmacies under the supervision of registered pharmacists. Illegal sale or possession of Part I 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: 2186 9845

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.