Drug News
藥 物 情 報

Issue Number 70

This is a monthly digest of local and overseas drug safety news released by the Drug Office of the Department of Health in August 2015 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

US: Gilenya (fingolimod) - FDA warns about cases of rare brain infection

On 4 August 2015, the US Food and Drug Administration (FDA) was warning that a case of definite progressive multifocal leukoencephalopathy (PML) and a case of probable PML have been reported in patients taking Gilenya (fingolimod) for multiple sclerosis (MS). These were the first cases of PML reported in patients taking Gilenya who had not been previously treated with an immunosuppressant drug for MS or any other medical condition. As a result, information about these recent cases is being added to the drug label.

Gilenya is an immunomodulator shown to benefit patients with relapsing forms of MS. This type of MS causes attacks or relapses, which are periods of time when symptoms get worse. Immunomodulators alter the immune system to reduce inflammation. PML is a rare and serious brain infection caused by the John Cunningham (JC) virus. The JC virus is a common virus that is harmless in most people but can cause PML in some patients who have weakened immune systems, including those taking immunosuppressant drugs.

At Drug Safety Communication in August 2013, FDA reported that a patient developed PML after taking Gilenya. PML could not be conclusively linked to Gilenya in this case because prior to Gilenya treatment the patient had been treated with an immunosuppressant drug that can cause PML and during Gilenya treatment the patient had received multiple courses of intravenous corticosteroids, which can weaken the immune system.

Patients taking Gilenya should contact their healthcare professionals right away if they experience symptoms such as new or worsening weakness; increased trouble using their arms or legs; or changes in thinking, eyesight, strength, or balance. Patients should not stop taking Gilenya without first discussing it with their healthcare professionals. Healthcare professionals should stop Gilenya on their patients and perform a diagnostic evaluation if PML is suspected.

In Hong Kong, Gilenya Hard Capsules 0.5mg (HK-61192) is a pharmaceutical product registered by Novartis Pharmaceuticals (HK) Ltd (Novartis), and is a prescription only medicine. Related news has been released by the FDA, and was reported on the Drug News Issue No. 46. As on 18 September 2015, the Department of Health (DH) has not received any adverse drug reaction (ADR) case related to fingolimod. Novartis has applied to the DH to update the package insert of the product to include the relevant warning, and the application is under evaluation. In view of the latest announcement by the US FDA on update of label, a letter to healthcare professionals was issued to draw their attention to the warning on 5 August 2015. The matter will be discussed in the meeting of the Pharmacy and Poisons (Registration of Pharmaceutical Products and Substances: Certification of Clinical Trial/Medicinal Test) Committee (the Registration Committee) of the Pharmacy and Poisons Board.

Taiwan: Clopidogrel risk communication components

It was noted from Taiwan Food and Drug Administration (FDA) website on 5 August 2015 that it has published a few adverse drug reactions in

connection with the use of clopidogrel. In recent years of reports received, suspected Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS) of the case, and some serious consequences as a death case, are due to the use of drugs containing clopidogrel. Therefore, medical personnel should take the initiative to inform the patient about the occurrence of skin and mucous membranes, that they should immediately withdraw and return the medicine to the clinic prescribers.

The Taiwan FDA has stated:

- After investigation, the manufacturer (Sanofi Co., Ltd.) of brand product Plavix containing clopidogrel has already included the side effects in Chinese version of the “vesicular rash (toxic epidermal necrosis, Stevenson - Johnson & Johnson's syndrome, polymorphic erythema, acute generalized rash pustular disease (AGEP)), angioedema, redness or flaking rash, urticaria, drug-induced anaphylaxis, drug rash associated with increased eosinophils and systemic symptoms (DRESS)”and related information on the leaflet.

- In order to alert medical professional’s attention, the Taiwan FDA will require product containing same ingredient should have the publications of the adverse effects of the Stevens- Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS) and other adverse reactions should be included in the product leaflet.

In Hong Kong, there are 32 registered pharmaceutical products containing clopidogrel, and are prescription only medicines. As on 18 September 2015, the DH has received one case of ADR on clopidogrel, and it is not related to the reactions to SJS / TEN / DRESS. In view of the announcement of the Taiwan FDA, the matter will be discussed in the meeting of the Registration Committee of the Pharmacy and Poisons Board.

Taiwan: Clozapine risk communication components

It was noted from Taiwan FDA website on 5 August 2015 that it has published a few adverse drug reactions in connection with the use of clozapine. In recent years of reports received, there were suspected bowel dysfunction, which were due to severe cases of intestinal obstruction (ileus) and ischemic bowel disease (ischemic bowel disease) and death. When clozapine has anticholinergic effects, it may lead to constipation and other issues such as severe intestinal complications. It reminds prescribers that the adjustment rate of the dose of clozapine should not be too fast. It also warns them that patients with gastrointestinal symptoms, immediate early response to intestinal obstruction or ischemic bowel disorders of serious adverse reactions may occur.

The Taiwan FDA has stated:

- After investigation, the manufacturer (Taiwan Novartis AG) of brand product Clozaril containing clozapine has already included the content in Chinese version of "the drug will be accompanied by various degrees of bowel dysfunction, from constipation to intestinal obstruction, fecal pressed and paralytic ileus, in very few of these conditions may result in death" and other related information in the “warning and precautions” of the leaflet.

- In order to alert medical professional’s attention, the Taiwan FDA will require the publications of the following adverse effects in Chinese version: “this drug had caused ischemic bowel disease (ischemic bowel disease) and death, therefore please pay attention on the use of doses” be included in the product leaflet.

In Hong Kong, there are seven registered pharmaceutical products containing clozapine, and are prescription only medicines. As on 18 September 2015, the DH has received two ADRs cases on clozapine, and they were not related to gastrointestinal adverse effect. In view of the announcement of the Taiwan FDA, the matter will be discussed in the meeting of the Registration Committee of the Pharmacy and Poisons Board.

Taiwan: Notice on re-evaluation of safety result on the product containing bromocriptine, and "product containing bromocriptine should publish additional required information" related issue

It was noted from Taiwan FDA website on 5 August 2015 that statistics has shown drug-containing bromocriptine for postpartum lactation suppression of serious or fatal adverse reactions reported an increase, especially cardiovascular, neurological and psychiatric-related side effects. To ensure patient safety after medication, the Taiwan FDA was pooling relevant information and drug-containing bromocriptine should revise the product leaflet and contents under (1) Indications; (2) Contraindications; and (3) The warnings and precautions; accordingly. Details of the requirement is at the website of:

http://www.fda.gov.tw/TC/newsContent.aspx?id=13927&chk=a25e7f96-2635-4bcc-bc27-4ec8b783a811&param=pn#.VhR4SUzyycw

In Hong Kong, there are six registered pharmaceutical products containing bromocriptine, and are prescription only medicines. Related news has been released by the European Medicines Agency (EMA), and was reported on the Drug News Issues No. 57 and 58. A letter to healthcare professionals to draw their attention to the new safety information was issued on 14 July 2014. As on 18 September 2015, the DH has not received any ADR case on bromocriptine. The matter was discussed in the meeting of the Registration Committee of the Pharmacy and Poisons Board on February 2015. The Committee decided that the sales pack labels and/or package inserts should be updated to include the relevant safety information:

For products containing bromocriptine 2.5mg:
1. Under "indications" if the registered pharmaceutical product is indicated for inhibition of lactation:
Inhibition of lactation for medical reasons:
Bromocriptine should only be used orally in strengths up to 2.5mg to inhibit lactation when medically indicated, such as in case of intrapartum loss, neonatal death or HIV infection of the mother. Products with strengths of 5 or 10mg are not indicated for such use.

BROMOCRIPTINE should not be used for the routine suppression of lactation, nor for the relief of symptoms of post-partum pain and engorgement, which can be adequately treated with non-pharmacological intervention (such as firm breast support, ice application) and simple analgesics.

2. Under "Contraindications"
"Product Name" is contraindicated for patients with uncontrolled hypertension, hypertensive disorders of pregnancy (including eclampsia, pre-eclampsia or pregnancy-induced hypertension), hypertension post-partum and in the puerperium, a history of coronary artery disease or other severe cardiovascular conditions, or a history of severe psychiatric disorders.

3. Under "Warnings and precautions"
Blood pressure should be carefully monitored, especially during the first day of therapy. If hypertension, suggestive chest pain, severe, progressive, or unremitting headache (with or without visual disturbance) or evidence of central nervous system toxicity develops, treatment should be discontinued and the patient evaluated promptly.

Taiwan: For injectable pharmaceutical composition containing midazolam drug safety-related matters

On 6 August 2015, the Taiwan FDA announced in the website that it has published a few adverse drug reactions in connection with the use of injectable midazolam. In recent years of reports received, suspected death occurred because of cases of respiratory depression. In order to avoid the similar tragedy from happening again, appropriate resuscitation equipment should be equipped and trained emergency medical personnel should be present during the usage of injectable midazolam. To ensure patient's safety, the recommended dosage for different indications shall be administered in accordance with the instruction sheet.

In Hong Kong, there are 11 registered pharmaceutical products containing midazolam, 7 of them are injections and the product information already contained reminder on the adverse reaction of respiratory depression. All products are prescription only medicines. As on 18 September 2015, the DH has received 20 ADRs cases on midazolam injection, and they were not related to

respiratory depression. The DH will remain vigilant on any safety information on midazolam.

Singapore: Prolia (denosumab 60mg) and Xgeva (denosumab 120mg) – Clinically significant cases of hypercalcaemia after cessation of treatment with denosumab in paediatric patients

On 14 August 2015, GlaxoSmithKline (GSK) Pte Ltd informed healthcare professionals of important new safety information in paediatric patients with growing skeletons who were being administered denosumab. Weeks to months following denosumab discontinuation in patients with growing skeletons, cases of clinically significant hypercalcaemia in patients presenting with nausea and vomiting with or without acute renal failure, requiring hospitalisation, have been observed as part of routine safety review by Amgen, the manufacturer of denosumab and GSK's partner in Singapore.

Healthcare professionals are advised to monitor for the development of hypercalcaemia following discontinuation of denosumab treatment in those patients with growing skeletons at the time of initiating treatment with denosumab.

In Hong Kong, there are three registered pharmaceutical products containing denosumab, namely Xgeva Solution for Injection 120mg (HK-61163), 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). All products are registered by GSK, and are prescription only medicines. As on 18 September 2015, the DH has received one case of ADR on Xgeva and two cases of ADRs on Prolia, and none of them were related to hypercalcaemia. GSK notified the Department of Health (DH) that a "Dear Healthcare Professional Letter" to local healthcare professionals to inform them of the warning had been issued on 6 July 2015, and the information was posted on the DH website on the same day. As previously reported, DH will maintain close contact with GSK to monitor any action deemed necessary and keep vigilant on any safety updates of the drug.

US: FDA warns that DPP-4 inhibitors for type 2 diabetes may cause severe joint pain

On 28 August 2015, the FDA issued warning that the type 2 diabetes medicines sitagliptin, saxagliptin, linagliptin and alogliptin may cause joint pain that can be severe and disabling. A new Warning and Precaution about this risk has been added to the label of all medicines in this drug class, called dipeptidyl peptidase-4 (DPP-4) inhibitors.

In a search of its adverse event database and the medical literature, FDA identified cases of severe joint pain associated with the use of DPP-4 inhibitors. Patients started having symptoms from 1 day to years after they started taking a DPP-4 inhibitor. After the patients discontinued the DPP-4 inhibitor medicine, their symptoms were relieved, usually in less than a month. Some patients developed severe joint pain again when they restarted the same medicine or another DPP-4 inhibitor.

Patients should not stop taking their DPP-4 inhibitor medicine, but should contact their healthcare professional right away if they experience severe and persistent joint pain. Healthcare professionals should consider DPP-4 inhibitors as a possible cause of severe joint pain and discontinue the drug if appropriate.

In Hong Kong, there are 32 registered pharmaceutical products which belongs to the DPP-4 inhibitors, including sitagliptin, saxagliptin, linagliptin, alogliptin and vildagliptin. All the products are prescription only medicines. As on 18 September 2015, the DH has received one case of ADR on sitagliptin, one case of ADR on linagliptin and two cases of ADRs on vildagliptin. The case of sitagliptin is related to the knee pain / blood glucose fluctuation and drug ineffective. None of them are related to joint pain. In view of new safety warning issued, a letter to inform the healthcare professionals was issued on 31 August 2015, and the matter will be discussed by the Registration Committee of the Pharmacy and Poisons Board.

Batch recall of Anexate 0.5mg/5ml Injection (HK-30501)

On 21 August 2015, the DH endorsed a licensed drug wholesaler, Roche Hong Kong Ltd. (Roche), to recall one batch of Anexate 0.5mg/5ml Injection from the market due to a quality issue.

The DH received notification from Roche that the manufacturer in France is conducting a voluntary recall on certain batches of the product following particulate matters found in one ampoule of the product.

Anexate 0.5mg/5ml Injection (containing flumazenil) is a prescription only medicine and used as an antidote due to benzodiazepines intoxication.

According to Roche, 18 boxes (containing 5 injections per box) from the affected batch have been supplied to the Hospital Authority (HA) but none of these 18 boxes were used. As on 18 September 2015, the DH has not received any adverse reaction report concerning the product. The DH closely monitored the recall. A notice was released on the website of the Drug Office on the same day to alert the public of the recall.

DH endorses batch recalls of Bactroban Nasal Ointment 3g (HK-33588)

On 24 August 2015, the DH endorsed a licensed drug wholesaler, GlaxoSmithKline Ltd (GSK), to recall two batches (batch number: C686773 and C704712) of Bactroban Nasal Ointment 3g from the market due to a quality issue.

The DH was notified by GSK that the above pharmaceutical product's manufacturer in the United Kingdom was recalling certain batches as there was a potential risk of physical contamination with foreign materials associated with the manufacturing of the active substance, mupirocin calcium. According to GSK, the risk posed by the finished product is low and the recall is a precautionary measure.

The above pharmaceutical product is an antibiotic indicated for nasal infection. It can only be sold in pharmacies under the supervision of registered pharmacists upon a doctor's prescription.

GSK revealed that 15,815 tubes from the two affected batches have been supplied to the local market, including the DH's clinics, the HA, private hospitals, private doctors and local pharmacies. As on 18 September 2015, the DH has not received any adverse reaction reports related to this pharmaceutical product. The DH closely monitored the recall. A notice was released on the website of the Drug Office on the same day to alert the public of the recall.

People who have used this pharmaceutical product should consult healthcare professionals if in doubt or are feeling unwell after use.

Batch recall of Apo-Pregabalin 50mg Capsules (HK-62682)

On 26 August 2015, the DH endorsed a licensed drug wholesaler, Hind Wing Co. Ltd ("Hind Wing"), to recall one batch (batch number: KW3890) of Apo-Pregabalin 50mg Capsules from shelf due to quality issue.

Following the recall of one batch of the product on 13 April 2015, Hind Wing notified the DH today that the Canadian manufacturer of the product is recalling another batch because an unidentified impurity was found out of specification in the above -mentioned batch during the stability testing.

Apo-Pregabalin 50mg Capsules, containing pregabalin, is a prescription medicine used for the treatment of epilepsy and neuropathic pain.

According to Hind Wing, 110 boxes of 30 capsules of the affected batch had been supplied to private doctors and local pharmacies. As on 18 September 2015, the DH has not received any adverse reports in connection with the product concerned. The DH closely monitored the recall. A notice was released on the website of the Drug Office on the same day to alert the public of the recall.

Drug Recall

Batch recall of Apo-Fluoxetine 10mg and 20mg Capsules (HK-41382 and HK-41383)

On 26 August 2015, the DH endorsed a licensed drug wholesaler, Hind Wing Co. Ltd ("Hind Wing"), to recall respectively two batches (batch numbers: KT8937 and MC5453) of Apo-Fluoxetine 10mg Capsules, and two batches (batch numbers: KT8933 and KZ8596) of Apo-Fluoxetine 20mg Capsules, at retailer level due to potential safety issue.

Following the recall of Apo-Fluoxetine 20mg Capsules on 20 April 2015, Hind Wing on 26 August 2015 notified the DH that the manufacturer in Canada was recalling further batches of the products because the active pharmaceutical ingredient used in the manufacturing of the affected batches may not meet the specification for the impurity (isobutyl vinyl ketone). Investigation by the manufacturer found that the cause of the impurity was due to lack of temperature controls during the synthesis process.

Apo-Fluoxetine 10mg and 20mg capsules, both containing fluoxetine, are prescription medicines used for the treatment of major depressive disorder.

According to Hind Wing, about 22,700 bottles of 100 capsules of the affected batches of Apo-Fluoxetine 10mg Capsules have been supplied to DH clinics, HA, private hospitals, private doctors and pharmacies since August 2014. About 2,160 bottles of 100 capsules of the affected batches of Apo-Fluoxetine 20mg Capsules have been supplied to private hospitals, private doctors and pharmacies since March 2014. As on 18 September 2015, the DH has not received any adverse reports in connection with the concerned products. The DH closely monitored the recall. A notice was released on the website of the Drug Office on the same day to alert the public of the recall.

Healthcare professionals and pharmacies are advised to stop supplying the affected batches of the products to patients. Members of the public who are taking the products should consult their doctors for advice.

Drug Incident

Woman arrested for suspected illegal sale of products with undeclared controlled drug substance on the Internet

On 21 August 2015, a joint operation was conducted by the DH and the Police for suspected illegal sale of two products (no English name) on the Internet which are suspected to contain an undeclared Part I poison.

Through the DH's surveillance system, samples of the above products were purchased previously from an Internet seller. Test results from the Government Laboratory revealed that the samples contained an undeclared Part I poison, diclofenac.

Diclofenac is a non-steroidal anti-inflammatory drug. Oral products containing diclofenac are prescription medicine for the relief of pain. They can only be supplied upon prescription at pharmacies under the supervision of a registered pharmacist. Side effects of diclofenac include gastrointestinal discomfort, nausea and peptic ulcers.

Members of the public who have purchased the above product should stop consuming them immediately. They should consult healthcare professionals for advice if they feel unwell or are in doubt after consuming the products.

Public urged not to buy or consume unlabelled slimming products with controlled ingredients

On 27 August 2015, the DH appealed to members of the public not to buy or consume unlabelled slimming products that may contain controlled medicine ingredients.

Upon the earlier investigation of public complaints, it was found that two local Internet sellers have been offering for sale various unlabelled slimming products obtained overseas.

Samples of the products were purchased for analysis and test results showed that some products contained Part I poisons including frusemide, fluoxetine, thyroxine and omeprazole.

The DH conducted joint operations with the Police against these Internet sellers on 26 August and 27 August. During the operations on both days, a 33-year-old woman and two 22-year-old men were respectively arrested for illegal sale of Part I poisons and unregistered pharmaceutical products.

Frusemide is used for the treatment of heart diseases and its side effects include low blood pressure and electrolyte imbalance. Fluoxetine is used for treatment of mood disorder and may cause hallucination and insomnia. Thyroxine is used for the treatment of hypothyroidism and its side effects include fast/irregular heart beat and hypertension. Omeprazole is used for managing gastric and duodenal diseases and may cause nausea, vomiting, abdominal pain and diarrhoea. Medicines containing these ingredients should only be supplied by pharmacies under the supervision of a registered pharmacist.

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: 2319 6319

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,
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