



Drug

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News

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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 March 2016 with relevant information update before publish. For the latest news and information, please refer to public announcements or the website of the Drug Office of the Department of Health (<http://www.drugoffice.gov.hk>).

Safety Update

EU: EMA recommends new safety measures for Zydelig. Measures include close monitoring and use of antibiotics to prevent pneumonia

On 18 March 2016, the European Medicines Agency (EMA) Pharmacovigilance Risk Assessment Committee (PRAC) issued provisional advice for doctors and patients using the cancer medicine Zydelig (idelalisib) to ensure that it continues to be used as safely as possible.

The PRAC recommends that all patients treated with Zydelig should receive antibiotics to prevent lung infection. Patients should also be monitored for infection and have regular blood tests for white cell counts because low counts can increase their risk of infection. Zydelig should not be started in patients with a generalised infection. It should also not be started in previously untreated patients with chronic lymphocytic leukaemia whose cancer cells have certain genetic mutations.

These are provisional recommendations which the PRAC has issued, as a precaution, to protect patients while the medicine is being reviewed. Once the review is concluded, EMA will communicate further and provide guidance to patients and healthcare professionals.

The review started after a higher rate of serious adverse events was seen in three clinical trials among patients receiving Zydelig compared with placebo. The adverse events included deaths related to infections such as pneumonia. The clinical trials, which have now been stopped, involved patients with chronic lymphocytic leukaemia and indolent

non-Hodgkin lymphoma. However, these studies did not use the medicine in the same way as currently authorised.

In Hong Kong, Zydelig Tablets 100mg (HK-64093) and Zydelig Tablets 150mg (HK-64094) are pharmaceutical products registered by Gilead Sciences Hong Kong Limited (Gilead), and are prescription only medicines. News on serious adverse effects including deaths was previously issued by the EMA, the Therapeutic Goods Administration (TGA) and Health Canada. The Department of Health (DH) issued a letter to inform local healthcare professionals on 14 March 2016. As on 27 May 2016, DH has not received any adverse drug reaction (ADR) case related to the products. As EMA, TGA and Health Canada are reviewing information to assess what further action is needed, DH will remain vigilant on the conclusions of the reviews and any safety updates from other overseas drug regulatory authorities.

EU: EMA reviews direct-acting antivirals for hepatitis C (interferon-free)

On 18 March 2016, EMA announced that a review of medicines known as direct-acting antivirals used for treating chronic (long-term) hepatitis C (an infectious disease that affects the liver, caused by the hepatitis C virus) has been started.

The following direct-acting antivirals have been approved in the EU for treating chronic hepatitis C: Daklinza (daclatasvir), Exviera (dasabuvir), Harvoni (sofosbuvir / ledipasvir), Olysio (simeprevir), Sovaldi (sofosbuvir) and Viekirax (ombitasvir / paritaprevir / ritonavir). They work by

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blocking the action of proteins in the hepatitis C virus which are essential for it to make new viruses.

Direct-acting antivirals are important medicines for the treatment of chronic hepatitis C and can be used without interferons, which are less well tolerated. Until recently, interferons were part of treatment regimens for hepatitis C. Interferons are known to act against both hepatitis B and C viruses, which may be present at the same time in some patients.

The review follows cases of hepatitis B re-activation in patients who have been infected with hepatitis B and C viruses, and who were treated with direct-acting antivirals for hepatitis C. Hepatitis B re-activation refers to a return of active infection in a patient whose hepatitis B infection had been inactive.

EMA will now assess the extent of hepatitis B re-activation in patients treated with direct-acting antivirals for hepatitis C and evaluate whether any measures are needed to optimise the treatment. While the review is ongoing, patients should speak to their doctor or pharmacist if they have any questions or concerns.

In Hong Kong, Harvoni Tablets [sofosbuvir/ledipasvir (HK-63886)], Sovaldi Tablets 400mg [sofosbuvir (HK-63501)] and Viekira Pak Tablets [ombitasvir/ paritaprevir/ ritonavir/ dasabuvir (HK-63695)] are registered pharmaceutical products. All these products are prescription only medicines. There is no registered pharmaceutical product containing daclatasvir or simeprevir. As on 27 May 2016, DH has received two cases and ten cases of ADR in connection with Sovaldi and Viekira Pak respectively, but none of them was related to hepatitis B re-activation. Since EMA's review is ongoing, DH will remain vigilant on the conclusion of the review and any safety updates from other overseas drug regulatory authorities.

US: FDA warns about several safety issues with opioid pain medicines; requires label changes

On 22 March 2016, the U.S. Food and Drug Administration (FDA) warned about several safety issues with the entire class of opioid pain medicines. These safety risks are potentially harmful interactions with numerous other

medications, problems with the adrenal glands, and decreased sex hormone levels. FDA is requiring changes to the labels of all opioid drugs to warn about these risks.

- Opioids can interact with antidepressants and migraine medicines to cause a serious central nervous system reaction called serotonin syndrome, in which high levels of the chemical serotonin build up in the brain and cause toxicity.
- Taking opioids may lead to a rare, but serious condition in which the adrenal glands do not produce adequate amounts of the hormone cortisol. Cortisol helps the body respond to stress.
- Long-term use of opioids may be associated with decreased sex hormone levels and symptoms such as reduced interest in sex, impotence, or infertility.

Opioids are a class of powerful narcotic pain medicines that are used to treat moderate to severe pain that may not respond well to other pain medicines. They can help manage pain when other treatments and medicines are not able to provide enough pain relief, but they also have serious risks including misuse and abuse, addiction, overdose, and death. Opioid medicines approved in the U.S. contain the following ingredients: alfentanil, buprenorphine, butorphanol, codeine, dihydrocodeine, fentanyl, hydrocodone, hydromorphone, meperidine, methadone, morphine, oxycodone, oxymorphone, pentazocine, remifentanyl, sufentanyl, tapentadol or tramadol.

Recommendations and information for patients and health care professionals are as follows:

a. Serotonin syndrome:

Patients taking an opioid along with a serotonergic medicine should seek medical attention immediately if they develop symptoms such as agitation; hallucinations; rapid heart rate; fever; excessive sweating; shivering or shaking; muscle twitching or stiffness; trouble with coordination; and/or nausea, vomiting, or diarrhea. Symptoms generally start within several hours to a few days of taking an opioid with another medicine that increases the effects of serotonin in the brain, but symptoms may occur later, particularly after a dose increase.

Health care professionals should discontinue opioid

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treatment and/or use of the other medicine if serotonin syndrome is suspected.

Cases of serotonin syndrome in the FDA Adverse Event Reporting System (FAERS) database were reported more frequently with the opioids fentanyl and methadone used at the recommended doses. Therefore, FDA is requiring a new statement in the Warnings and Precautions section to be added to these drug labels. Some opioids, including tramadol, tapentadol, and meperidine, already have warnings about serotonin syndrome. Cases were also reported with other opioids, so the labels of all these drugs will be updated to include information about serotonin syndrome in the Drug Interactions and Adverse Reactions sections.

b. Adrenal insufficiency:

Patients should seek medical attention if they experience symptoms of adrenal insufficiency such as nausea, vomiting, loss of appetite, fatigue, weakness, dizziness, or low blood pressure. Health care professionals should perform diagnostic testing if adrenal insufficiency is suspected. If diagnosed, treat with corticosteroids and wean the patient off of the opioid, if appropriate. If the opioid can be discontinued, follow-up assessment of adrenal function should be performed to determine if treatment with corticosteroids can be discontinued.

FDA is requiring a new statement about adrenal insufficiency to be added to the Warnings and Precautions section of all opioid labels.

c. Decreased sex hormone levels:

Patients should inform their health care professionals if they experience symptoms of low libido, impotence, erectile dysfunction, lack of menstruation, or infertility. Health care professionals should conduct laboratory evaluation in patients presenting with such signs or symptoms.

FDA reviewed published studies that assessed levels of sex hormones in patients taking opioids chronically; however, all had limitations that make it difficult to determine whether the symptoms were caused by the opioids or other factors. The labels of some opioids already describe this possible risk, and FDA is now adding consistent

information to the Adverse Reactions section of all opioid labels.

In Hong Kong, opioid medicines are registered pharmaceutical products containing the following ingredients: alfentanil (1 product), buprenorphine (8 products), codeine (329 products), dihydrocodeine (10 products), fentanyl (11 products), methadone (5 products), morphine (23 products), oxycodone (13 products), remifentanyl (6 products), sufentanyl (2 products), tapentadol (8 products) and tramadol (45 products). There is no registered pharmaceutical product containing butorphanol, hydrocodone, hydromorphone, meperidine, oxymorphone or pentazocine. As on 27 May 2016, DH has received one case and two cases of ADR in connection with morphine and tramadol respectively, but the cases were not related to serotonin syndrome, adrenal insufficiency or decreased sex hormone levels. In view of the above FDA announcement, DH issued a letter to inform local healthcare professionals on 23 March 2016, and the matter will be discussed by the Registration Committee of the Pharmacy and Poisons Board.

Singapore: Role of HLA-B*5801 genotyping prior to initiation of allopurinol

On 23 March 2016, Ministry of Health (MOH) and the Health Sciences Authority (HSA) of Singapore informed healthcare professionals that routine genotyping for the HLA-B*5801 allele prior to the initiation of allopurinol therapy is not required as standard of care in Singapore. The basis for this recommendation took into consideration the low Positive Predictive Value (PPV) of 2.4% of HLA-B*5801 for allopurinol-induced Serious Cutaneous Adverse Reactions (SCAR), limited alternative urate-lowering therapies (ULTs), and the unfavourable cost-effectiveness analysis based on current data. Genotyping may be considered in patients who have other pre-existing risk factors such as renal impairment to identify patients at high risk of allopurinol-induced SCAR. Healthcare professionals are advised to use allopurinol with caution. Genetic testing should not substitute for appropriate clinical vigilance and patient management.

In Hong Kong, there are 46 registered pharmaceutical products containing allopurinol. All these products are pharmacy only medicines. As on

27 May 2016, DH has received two cases of ADR in connection with allopurinol, and both of them involved Stevens-Johnson syndrome. DH will remain vigilant on the safety of medicines containing allopurinol.

Canada: Health Canada reminds parents not to give cough and cold medication to children under 6 years old

On 24 March 2016, Health Canada reminded Canadians that over-the-counter cough and cold medicines should not be given to children under the age of 6. Cough and cold medicines include the following ingredients:

- Antihistamines in cough and cold medicines (used to treat sneezing, runny nose): brompheniramine maleate, chlorpheniramine maleate, clemastine hydrogen fumarate, dexbrompheniramine maleate, diphenhydramine hydrochloride, diphenylpyraline hydrochloride, doxylamine succinate, pheniramine maleate, phenyltoloxamine citrate, promethazine hydrochloride, pyrilamine maleate, triprolidine hydrochloride;
- Antitussives (used to treat cough): dextromethorphan, dextromethorphan hydrobromide, diphenhydramine hydrochloride;
- Expectorants (used to loosen mucus): guaifenesin (glyceryl guaiacolate);
- Decongestants (used to treat congestion): ephedrine hydrochloride/sulphate, phenylephrine hydrochloride/sulphate, pseudoephedrine hydrochloride/sulphate

In 2009, Health Canada conducted a review and determined over-the-counter cough and cold products in children have not been shown to be effective. In addition, serious harm, including misuse, overdose and side-effects may occur in children under 6 years of age when using over-the-counter cough and cold products, although the risk of such serious harm is low. Despite recommendations and labelling on these products, recent reports indicate that children under 6 are still being given cough and cold medications by parents or caregivers.

Health Canada reminds parents and caregivers of

the following:

- Do not use over-the-counter cough and cold medicines in children under 6.
- Always check the label first to make sure the medication is suitable for their child.
- Do not give children medications labelled only for adults.
- Do not give children aged 6 and up more than one kind of cough and cold medicine (unless under the advice of a healthcare practitioner). Combining medicines with the same ingredient(s) may cause side effects.
- Talk to their health care practitioner (e.g. doctor, pharmacist, nurse, etc.) if they have any questions about using cough and cold medicines in children. These professionals can also help make sure there are no interactions with other health products their child may be taking.
- A cold is not the same as the flu. Cold medications are not effective against the flu.

In Hong Kong, cough and cold medicines are registered pharmaceutical products. As on 27 May 2016, DH has received eight ADR cases in connection with cough and cold medicines containing the above ingredients, and one of the case was related to a 9 month old baby girl. In April 2009, the Registration Committee of the Pharmacy and Poisons Board decided that labels and package inserts of cough and cold medicines should not contain dosage instructions or other references to their use by children under 6 years of age. DH will remain vigilant on the safety of cough and cold medicines.

Singapore: Tasigna® (nilotinib) - Need to screen patients for hepatitis B virus (HBV) infection before treatment due to risk of HBV reactivation

On 28 March 2016, the HSA announced that Novartis would like to inform healthcare professionals of the risk of hepatitis B (HBV) reactivation associated with the use of Tasigna® (nilotinib) in patients who are chronic HBV carriers.

Cases of reactivation of HBV can occur in patients who are chronic carriers of this virus after receiving BCR-ABL tyrosine kinase inhibitors (TKIs), such

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as nilotinib. Case reports indicate that HBV reactivation may occur at any time during BCR-ABL TKIs treatment. Some of these cases resulted in acute hepatic failure or fulminant hepatitis leading to liver transplantation or a fatal outcome.

Healthcare professionals are advised of the following:

- Patients should be tested for HBV infection before initiating treatment with nilotinib.
- Patients currently on nilotinib should have baseline testing for HBV infection in order to identify chronic carriers of the virus.
- Experts in liver disease and in the treatment of HBV should be consulted before treatment is initiated in patients with positive HBV serology (including those with active disease) and for patients who test positive for HBV infection during treatment.
- Carriers of HBV who require treatment with nilotinib should be closely monitored for signs and symptoms of active HBV infection throughout therapy and for several months following termination of therapy.

The package inserts for Tasigna® products in Singapore have been updated with the new information.

In Hong Kong, Tasigna Cap 150mg (HK-60833) and Tasigna Cap 200mg (HK-56797) are registered pharmaceutical products, and are prescription only medicines which are registered by Novartis Pharmaceuticals (HK) Limited (Novartis). As on 27 May 2016, DH has not received any ADR case related to the products. Novartis confirmed with DH that letters to inform healthcare professionals of the above matter has been issued by the company on 14 April 2016. In view of the HSA announcement, DH issued a letter to inform local healthcare professionals on 31 March 2016, and the matter will be discussed by the Registration Committee of the Pharmacy and Poisons Board.

Singapore: Glivec® (imatinib) - Need to screen patients for hepatitis B virus (HBV) infection before treatment due to risk of HBV reactivation

On 28 March 2016, the HSA announced that

Novartis would like to inform healthcare professionals of the risk of HBV reactivation associated with the use of Glivec® (imatinib) in patients who are chronic HBV carriers.

Cases of reactivation of HBV can occur in patients who are chronic carriers of this virus after receiving BCR-ABL TKIs, such as imatinib. Case reports indicate that HBV reactivation may occur at any time during BCR-ABL TKIs treatment. Some of these cases resulted in acute hepatic failure or fulminant hepatitis leading to liver transplantation or a fatal outcome.

Healthcare professionals are advised of the following:

- Patients should be tested for HBV infection before initiating treatment with imatinib.
- Patients currently on imatinib should have baseline testing for HBV infection in order to identify chronic carriers of the virus.
- Experts in liver disease and in the treatment of HBV should be consulted before treatment is initiated in patients with positive HBV serology (including those with active disease) and for patients who test positive for HBV infection during treatment.
- Carriers of HBV who require treatment with imatinib should be closely monitored for signs and symptoms of active HBV infection throughout therapy and for several months following termination of therapy.

The package inserts for Glivec® products in Singapore have been updated with the new information.

In Hong Kong, Glivec Cap 100mg (HK-49431) is a registered pharmaceutical product, and is a prescription only medicine registered by Novartis. As on 27 May 2016, DH has received three ADR cases in connection with the product, but neither of them was related to HBV reactivation. Novartis confirmed with DH that letters to inform healthcare professionals of the above matter has been issued by the company on 14 April 2016. In view of the HSA announcement, DH issued a letter to inform local healthcare professionals on 31 March 2016, and the matter will be discussed by the Registration Committee of the Pharmacy and Poisons Board.

Drug Recall

DH endorsed batch recall of Natural-Pharm Rose Hips C Tablets 500mg wrongly packed as Natural-Pharm Rose Hips C Tablets 1000mg

On 18 March 2016, DH endorsed a licensed drug wholesale dealer, Cera Y C Company Limited (Cera), to recall one batch of Natural-Pharm Rose Hips C Tablets 500 mg, which wrongly labeled as Natural-Pharm Rose Hips C Tablets 1000mg (batch number: 140303) on the outer box, from shelves.

Upon a public complaint, DH found that an incorrect outer box has been used to pack a batch of Natural-Pharm Rose Hips C Tablets 500mg (HK-41797) by the local supplier. On the outer box of this batch of product, it is labeled as Natural-Pharm Rose Hips C Tablets 1000mg (HK-41796; batch number 140303) while the bottle label and the package insert were correctly labeled as Natural-Pharm Rose Hips C Tablets 500mg (HK-41797).

The product is an over-the-counter product containing vitamin C. According to Cera, the product was supplied to medicine stores and pharmacies.

A notice was released on the website of the Drug Office on the same day to alert the public of the recall.

DH endorsed recall of four batches of Cinnarizine Tablet 25mg

On 22 March 2016, DH endorsed a licensed drug wholesaler, Star Medical Supplies Ltd, to recall four batches of Cinnarizine Tablet 25mg (HK-12005) (batch numbers: M40594/1, M40594/2, 150282/1 and 150282/2) from the market because of a quality issue.

DH received notification from Star Medical that it has received complaints about black spots found on certain cinnarizine tablets. The black spots were suspected to be foreign matter including plastic fragments and lubricant. The Italian manufacturer decided to recall four affected batches from the

market after preliminary investigation.

Cinnarizine Tablet is an over-the-counter medicine used for the treatment of motion sickness, nausea and vomiting. According to Star Medical, about 1,261 bottles (each bottle containing 1,000 tablets) from the affected four batches have been supplied to the Hospital Authority, one private hospital and private doctors. Star Medical had informed the above hospitals and doctors to stop supplying the affected batches of the products to patients.

As on 27 May 2016, DH has not received any ADR case related to the product.

A notice was released on the website of the Drug Office on the same day to alert the public of the recall.

A product containing any western drug ingredient must be registered under the Pharmacy and Poisons Ordinance before it can be sold in Hong Kong. Part 1 poisons should be sold at registered pharmacies under the supervision of registered pharmacists. Illegal sale or possession of Part 1 poisons and unregistered pharmaceutical products are offences under the Pharmacy and Poisons Ordinance (Cap 138). The maximum penalty is a fine of \$100,000 and two years' imprisonment for each offence. Antibiotics can only be supplied at registered pharmacies by registered pharmacists or under their supervision and upon a doctor's prescription. They should only be used under the advice of a doctor. Illegal sale or possession of antibiotics are offences under the Antibiotics Ordinance (Cap 137) and the maximum penalty is a \$30,000 fine and one year's imprisonment for each offence.

All registered pharmaceutical products should carry a Hong Kong registration number on the package in the format of "HK-XXXXX". The products mentioned in the above incidents were not registered pharmaceutical products under the Ordinance in Hong Kong. Their safety, quality and efficacy cannot be guaranteed. Members of the public were exhorted not to use products of unknown or doubtful composition. They should stop using the aforementioned products immediately if they had them in their possession and to consult healthcare professionals if they felt unwell after taking the products. The products should be destroyed or disposed properly, or submitted to the Department's Drug Office during office hours.

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,
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.