Drug News
藥 物 情 報

Issue Number 97

This is a monthly digest of local and overseas drug safety news released by the Drug Office of the Department of Health in November 2017 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: Febuxostat: FDA to evaluate increased risk of heart-related death

On 15 November 2017, the United States (US) Food and Drug Administration (FDA) alerted the public that preliminary results from a safety clinical trial show an increased risk of heart-related death with febuxostat (brand name Uloric) compared to another gout medicine called allopurinol. FDA required the Uloric drug manufacturer, Takeda Pharmaceuticals, to conduct this safety study when the medicine was approved in 2009. Once the final results from the manufacturer are received, FDA will conduct a comprehensive review and will update the public with any new information.

Febuxostat is FDA-approved to treat a type of arthritis called gout in adults. The febuxostat drug labels already carry a Warning and Precaution about cardiovascular events because the clinical trials conducted before approval showed a higher rate of heart-related problems in patients treated with febuxostat compared to allopurinol. These problems included heart attacks, strokes, and heart-related deaths. As a result, FDA required an additional safety clinical trial after the drug was approved and on the market to better understand these differences, and that trial was finished.

The safety trial was conducted in over 6,000 patients with gout treated with either febuxostat or allopurinol. The primary outcome was a combination of heart-related death, non-deadly heart attack, non-deadly stroke, and a condition of inadequate blood supply to the heart requiring urgent surgery. The preliminary results show that overall, febuxostat did not increase the risk of these combined events compared to allopurinol. However, when the outcomes were evaluated separately, febuxostat showed an increased risk of heart-related deaths and death from all causes.

Healthcare professionals are recommended to consider this safety information when deciding whether to prescribe or continue patients on febuxostat.

In Hong Kong, there are 2 registered pharmaceutical products containing febuxostat, namely Feburic Tablets 80mg (HK-61185) and Feburic Tablets 120mg (HK-61186) registered by Astellas Pharma Hong Kong Company Limited. Both products are prescription-only medicines. Their package inserts have already contained warnings and precautions about cardio-vascular disorders associated with the use of the products. The Department of Health (DH) will keep vigilant on any safety update of the drug.

Australia: Safety review: Codeine use in children and ultra-rapid metabolisers: Update - recommendations implemented

On 22 November 2017, the Therapeutic Goods Administration (TGA) of Australia advised consumers and health professionals that the recommendations of the safety review of codeine use in children and rapid metabolisers have been implemented. The Product Information documents for all prescription codeine products have been updated to reflect the findings of the TGA's safety review.

Specifically, codeine products should no longer be used in children under 12 years of age, or in children aged 12-18 years who have recently

undergone surgery to remove their tonsils or adenoids. Codeine should also not be used by breastfeeding mothers or in patients known to be ultra-rapid metabolisers.

In Hong Kong, there are 309 registered pharmaceutical products containing codeine which are classified according to the codeine concentration in the product, e.g. products containing codeine less than 0.2% are pharmacy-only medicines while products containing codeine 0.2% or more are prescription-only medicines. News on safe use of codeine preparation had been issued by various overseas drug regulatory authorities, and was reported in the Drug News Issue No. 34, 40, 44, 54, 65, 69 and 90. In connection with the safety updates, DH issued letters to inform local healthcare professionals to draw their attention on 16 August 2012, 7 June 2013 and 21 April 2017. As on 5 December 2017, DH has received one case of adverse drug reaction (ADR) related to codeine.

The Registration Committee of the Pharmacy and Poisons Board (the Registration Committee) decided in the meeting on 5 July 2013 that the sales packs and/or package inserts of pharmaceutical products containing codeine should be updated to include safety warnings on restriction on the use of codeine in children, breastfeeding mothers and ultra -rapid metabolisers. On 7 December 2017, the Registration Committee considered the latest warnings for oral preparations containing codeine, imposed by different drug regulatory authorities, including US FDA and TGA and decided that the sales pack labels and/or package inserts of registered pharmaceutical products containing codeine should include new contraindication and strengthened warning of codeine issued by the US FDA on 21 April 2017, and the latest recommendations in the above TGA's announcement.

UK: Quinine: reminder of dose-dependent QT-prolonging effects; updated medicine interactions

On 24 November 2017, the Medicines and Healthcare products Regulatory Agency (MHRA) of the United Kingdom (UK) announced that quinine has dose-dependent QT-interval-prolonging effects and should be used with caution in patients with risk factors for QT prolongation or in those with atrioventricular block.

Quinine is well known to have effects on the QT interval. A 2017 routine European Union (EU) review recommended that warnings for dose-dependent QT-prolonging effects should be present in the product information for all quinine-containing medicines.

Use caution if prescribing quinine medicines in patients with conditions that predispose to QT prolongation, such as pre-existing cardiac disease or electrolyte disturbances, or in patients taking other medicines that prolong the QT interval. Use caution when prescribing quinine to patients with atrioventricular block since quinine could aggravate conduction deficits.

Quinine is metabolised via hepatic oxidative cytochrome P450 pathways, predominantly by CYP3A4. The 2017 review identified a pharmacokinetic study reporting that serum levels of phenobarbital or carbamazepine could become raised when these anticonvulsant drugs are used concomitantly with quinine. Although data appear to be limited to this study, it is advisable to monitor for evidence of toxicity if quinine is used concomitantly.

In Hong Kong, there are 2 registered pharmaceutical products containing quinine. Both of them are prescription-only medicines. As on 5 December 2017, DH has not received any case of ADR related to quinine. In light of the above MHRA's announcement, DH issued a letter to inform local healthcare professionals to draw their attention on the above safety information on 27 November 2017 and the matter will be discussed by the Registration Committee.

UK: Oral tacrolimus products: reminder to prescribe and dispense by brand name only

On 24 November 2017, MHRA reminded healthcare professionals regarding prescribing and dispensing of oral tacrolimus products. Inadvertent switching between tacrolimus products has been associated with reports of toxicity and graft rejection. If prescribers switch a patient to a

different brand, ensure the patients receive careful supervision and therapeutic monitoring by an appropriate specialist.

Tacrolimus is an immunosuppressant drug that may be given orally to prevent or treat organ transplant rejection. Tacrolimus has a narrow therapeutic index, and even minor differences in blood levels have the potential to cause graft rejection reactions or toxicity.

In June 2012, MHRA issued a Drug Safety Update recommending that all oral tacrolimus products should be prescribed and dispensed by brand name only. Recommendations from June 2012 remain in place, and also apply to any new tacrolimus products launched since this advice was issued. This includes generic products and prolonged-release formulations.

In Hong Kong, there are 17 registered pharmaceutical products containing tacrolimus in oral dosage forms, and all are prescription-only medicines. Related news was previously released by MHRA and was reported in the Drug News Issue No. 31. DH issued a letter to inform local healthcare professionals to draw their attention on the issue on 25 May 2012. DH will remain vigilant on safety update of tacrolimus issued by other overseas drug regulatory authorities.

US: Biotin (Vitamin B7): May interfere with laboratory tests

On 28 November 2017, US FDA alerted the public, healthcare providers, laboratory personnel, and laboratory test developers that biotin can significantly interfere with certain laboratory tests and cause incorrect test results which may go undetected.

Biotin in blood or other samples taken from patients who are ingesting high levels of biotin in dietary supplements can cause clinically significant incorrect laboratory test results. FDA has seen an increase in the number of reported adverse events, including one death, related to biotin interference with laboratory tests.

Biotin in patient samples can cause falsely high or falsely low results, depending on the test. Incorrect test results may lead to inappropriate patient management or misdiagnosis. For example, a falsely low result for troponin, a clinically important biomarker to aid in the diagnosis of heart attacks, may lead to a missed diagnosis and potentially serious clinical implications. FDA has received a report that one patient taking high levels of biotin died following falsely low troponin test results when a troponin test known to have biotin interference was used.

Many laboratory tests use biotin technology due to its ability to bond with specific proteins which can be measured to detect certain health conditions. For example, biotin is used in hormone tests and tests for markers of cardiac health like troponin. Biotin, also known as vitamin B7, is a water-soluble vitamin often found in multi-vitamins, prenatal vitamins, and dietary supplements marketed for hair, skin, and nail growth.

FDA is aware of people taking high levels of biotin that would interfere with laboratory tests. Many dietary supplements promoted for hair, skin, and nail benefits contain biotin levels up to 650 times the recommended daily intake of biotin. Physicians may also be recommending high levels of biotin for patients with certain conditions such as multiple sclerosis. Biotin levels higher than the recommended daily allowance may cause interference with laboratory tests. Patients and physicians may be unaware of biotin interference in laboratory assays. Even physicians who are aware of this interference are likely unaware as to whether, and how much biotin, patients are taking. Since patients are unaware of biotin interference, patients may not report taking biotin supplements to their physicians, and may even be unware they are taking biotin (e.g., when taking products generally labeled for their benefits to hair and nails).

FDA is working with stakeholders to better understand biotin interference with laboratory tests, and to develop additional future recommendations for safe testing in patients who have taken high levels of biotin when using laboratory tests that use biotin technology. FDA is monitoring reports of adverse events associated with biotin interference with laboratory tests and will update the public if significant new information becomes available.

Safety Update

In Hong Kong, there are 258 registered pharmaceutical products containing biotin. As on 5 December 2017, DH has not received any case of ADR related to biotin. DH issued a letter to inform local healthcare professionals to draw their attention on the safety information concerning the laboratory test of patients taking biotin on 29 November 2017. DH will remain vigilant on safety update regarding biotin issued by other overseas drug regulatory authorities.

Drug Incident

Man arrested for suspected illegal sale of nicotine-containing liquids for electronic cigarettes

On 7 November 2017, a joint operation was conducted by DH and the Police in Tung Chung resulting in the arrest of a 28-year-old man for the illegal sale of two nicotine-containing liquids intended for use with electronic nicotine delivery systems, commonly known as electronic cigarettes.

Acting upon a public complaint, DH found that the above nicotine-containing liquids were offered for sale on a social networking website. Samples of the products were purchased for laboratory analysis. Test results from the Government Laboratory revealed that the samples contained nicotine, a Part 1 poison under the Pharmacy and Poisons Ordinance (Cap 138). During the operation, the seller was arrested by the Police for suspected illegal sale and possession of Part 1 poison and unregistered pharmaceutical products.

Smokers are advised to quit smoking for their own health and that of others. They are encouraged to make use of smoking cessation services through DH's Integrated Smoking Cessation Hotline (1833 183). Information on smoking cessation can also be obtained from the DH's Tobacco Control Office website (http://www.tco.gov.hk).

A notice was released on the website of Drug Office on 7 November 2017 to alert the public of the drug incident.

DH urged public not to buy or consume product with doubtful composition

On 24 November 2017, DH urged the public not to buy or consume a product (no English name, Chinese name: 大力仔) as it was found to contain an undeclared controlled ingredient.

Acting upon public enquiry, DH purchased a sample of the above product for analysis. Testing results from the Government Laboratory confirmed that the sample contained aminotadalafil, a Part 1 poison under the Pharmacy and Poisons Ordinance (Cap 138).

DH initiated a joint operation with the Police immediately and raided a retailer in Wan Chai. A man aged 35 was arrested by the Police for suspected illegal sale and possession of Part 1 poison.

Aminotadalafil is structurally similar to tadalafil, a prescription drug ingredient used for erectile dysfunction. It may interact with nitrates found in some drugs such as nitroglycerin and cause decrease in blood pressure to dangerous levels.

The public may visit the Drug Office's page for health message on sexual dysfunction and virility products and information on virility products found to contain undeclared Western medicines.

A notice was released on the website of Drug Office on 24 November 2017 to alert the public of the drug incident.

News in Brief

Adverse drug reaction report of suspected cardiac events associated with nivolumab

On 14 November 2017, the DH issued a letter to inform local healthcare professionals to draw their attention on the risk of myocarditis with Nivolumab, an anti-programmed death-1 antibody used in cancer treatment.

The appeal follows the review of our Adverse Drug Reactions (ADR) Reporting System database that identified three local cases of suspected cardiac events associated with Nivolumab. Two cases involved the development of arrhythmia (atrial fibrillation and heart block) after the use of nivolumab alone while the remaining case concerned myocarditis experienced by a patient who was on sequential therapy with ipilimumab and nivolumab. In these three cases, the causality of the events to nivolumab could not be completely excluded.

Nivolumab can cause clinically significant immune -mediated adverse reactions. Across clinical trials of Nivolumab administered as a single agent or in combination with ipilimumab, myocarditis was reported to occur in less than 1% of patients receiving Nivolumab.

Immune-mediated adverse reactions may occur after discontinuation of Nivolumab. For any suspected immune-mediated adverse reactions, adequate evaluation should be performed to confirm aetiology or exclude other causes. Based on the severity of the adverse reaction, Nivolumab or Nivolumab in combination with Ipilimumab should be withheld and corticosteroids administered.

In Hong Kong, there are 2 registered pharmaceutical products containing nivolumab, namely Opdivo Concentrate For Solution For Infusion 40mg/4ml (HK-64231) and Opdivo Concentrate For Solution For Infusion 100mg/10ml (HK-64232), and 2 products containing Ipilimumab, namely Yervoy Concentrate For Solution For Infusion 50mg/10ml (HK-63494) and Yervoy Concentrate For Solution For Infusion 200mg/40ml (HK-63495). All the above products are registered by Bristol-Myers Squibb Pharma (HK) Ltd and are prescription-only medicines. Risk of myocarditis has already been included in the package insert of Yervoy. The package insert of Opdivo will be updated to include the risk of myocarditis. As on 5 December 2017, the DH has just received the above ADR cases of suspected cardiac events on Nivolumab and Ipilimumab. DH will remain vigilant on the issue.

Please report any adverse events caused by drugs to the Pharmacovigilance Unit of the DH (tel. no.: 2319 2920, fax: 2319 6319 or email: adr@dh.gov.hk). For details, please refer to the "ADR Reporting" webpage of Drug Office (http://www.drugoffice.gov.hk/adr.html).

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.

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
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Link: http://www.drugoffice.gov.hk/adr.html
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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.