# Drug News
# 藥 物 情 報

**Issue Number 75**

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

### Singapore: Drug-drug interaction between repaglinide and clopidogrel: Potential risk of hypoglycaemia

It was noted from the Health Sciences Authority (HSA) website on 11 January 2016 that the findings of a recent study concluded that co-administration of repaglinide and clopidogrel results in an increased systemic exposure to repaglinide. This is due to strong inhibition of CYP2C8 by clopidogrel acyl-β-D-glucuronide. This could in turn enhance the glucose-lowering effect of repaglinide, thereby predisposing patients to the risk of hypoglycaemia.

Repaglinide (Novonorm®, Novo Nordisk Pharma (Singapore) Pte Ltd) is an oral antidiabetic agent that has been registered in Singapore since January 1999 for the treatment of adults with type 2 diabetes mellitus. Clopidogrel (Plavix®, Sanofi-Aventis Singapore Pte Ltd) is an antiplatelet agent that has been registered in Singapore since June 1998.

In a study conducted by Tornio et al, nine healthy subjects received clopidogrel (300mg on day 1, followed by 75mg daily for 2 consecutive days) or a single dose of placebo in a crossover manner. Repaglinide was co-administered as single dose of 0.25mg on days 1 and 3 of clopidogrel treatment and on the day of placebo administration. Co-administration of repaglinide and clopidogrel was shown to result in an increase in repaglinide systemic exposure (AUC0-∞) by 5.1-fold and 3.9-fold on days 1 and 3 of clopidogrel treatment, respectively, when compared with placebo ($p<0.001$). The elimination half-life of repaglinide was also observed to be prolonged by 42% and 22%, respectively ($p<0.005$). The blood glucose levels of study subjects were significantly lower in both clopidogrel phases as compared to placebo, reaching a minimum concentration of 3.3 ± 0.6mmol/L, 3.9 ± 0.6mmol/L and 4.4 ± 0.5mmol/L following administration of repaglinide 1 hour after dosing with clopidogrel 300mg (day 1), clopidogrel 75mg (day 3) or placebo, respectively.

This study also identified clopidogrel acyl-β-D-glucuronide, the metabolite of clopidogrel, as a potent time-dependent inhibitor of CYP2C8 in vitro. In view of the study findings, the study authors recommended that concomitant use of repaglinide and clopidogrel is best avoided. They also postulated that clopidogrel is likely to cause drug-drug interactions with other CYP2C8 substrates, such as montelukast, paclitaxel and pioglitazone, which warrant further clinical studies.

To date, HSA has not received any reports of hypoglycaemia associated with the concomitant use of repaglinide and clopidogrel. HSA is working with the companies to strengthen the package inserts of both products in Singapore to include warnings and precautions with regard to the potential risk of hypoglycaemia arising from their drug-drug interaction.

Healthcare professionals are advised to consider the above safety information when prescribing repaglinide and clopidogrel together, and to monitor for signs and symptoms of hypoglycaemia in patients taking concomitant repaglinide and clopidogrel.

In Hong Kong, there are 32 registered pharmaceutical products containing clopidogrel

and 8 registered pharmaceutical products containing repaglinide. All these products are prescription only medicines. Related news was previously issued by Health Canada, and was reported in the Drug News Issue No. 69. The Department of Health (DH) issued a letter to inform local healthcare professionals on 3 August 2015. The matter was discussed by the Registration Committee of the Pharmacy and Poisons Board (the Committee) on 4 December 2015. The Committee decided that the sales pack label or package insert should be updated to include the relevant warnings. As on 10 March 2016, DH has not received any adverse drug reaction (ADR) case resulting from drug-drug interaction between repaglinide and clopidogrel.

## Singapore: Risk of pancreatitis associated with the use of deferasirox in paediatric patients

It was noted from the HSA website on 11 January 2016 that overseas cases of pancreatitis have been reported in paediatric patients following treatment with deferasirox.

Deferasirox (Exjade®, Novartis (Singapore) Pte Ltd) is an orally active iron chelator that has been registered in Singapore since 2008. It is approved for the treatment of chronic iron overload, either due to frequent blood transfusions (≥ 7ml/kg/month of packed red blood cells) in patients aged 6 years and older with beta thalassaemia major, or in patients aged 10 years and older with non-transfusion-dependent thalassaemia syndromes. Exjade® is also approved for the treatment of chronic iron overload due to blood transfusions when deferoxamine therapy is contraindicated or inadequate in patients with other anaemias, in patients aged 2 to 5 years, as well as in patients with beta thalassaemia major with iron overload due to infrequent blood transfusions.

Acute pancreatitis is usually characterised by abdominal pain and an increase in pancreatic enzymes in the blood and urine, with an overall mortality of approximately 5%. Epidemiological studies suggest that drug-induced pancreatitis is relatively rare, with an estimated incidence of 0.1% to 2%. Although most cases of possible drug-induced pancreatitis are mild, some have been reported to be severe or even fatal.

The management of drug-induced pancreatitis includes the discontinuation of suspected drugs to prevent further progression of any ongoing pancreatic injury, intravenous fluid replacement, and close monitoring of blood pressure, cardiac and pulmonary status. In more severe cases, parenteral or enteral nutrition may be required if patients are unable to tolerate oral intake.

Recently, overseas adverse reaction reports received through the World Health Organisation (WHO) VigiBase® suggest a signal of pancreatitis associated with the use of deferasirox in paediatric patients.

As of March 2015, 14 reports of pancreatitis associated with the use of deferasirox in children and adolescents, aged between 4 to 16 years old, have been identified from VigiBase®. Deferasirox was the only suspected drug in 11 of these 14 cases. The remaining three cases also included other suspected drugs, such as azithromycin, ceftriaxone, hydroxycarbamide, amoxicillin, clarithromycin, omeprazole and deferoxamine. The time to onset was reported in nine cases and ranged from 17 days to over five years (median 11 months). This time interval is relatively consistent with the time to onset of drug-induced pancreatitis that had been reported in literature with various drugs including valproic acid, oestrogen, sulindac, statins and ACE inhibitors. In addition, a positive dechallenge was also noted in six cases, which is supportive of a drug-induced effect.

HSA has not received any reports of pancreatitis associated with the use of deferasirox in Singapore. The package insert for Exjade® is currently in the process of being strengthened to include warnings on the risk of acute pancreatitis.

Healthcare professionals are advised to take into consideration the potential risk of acute pancreatitis in patients who are prescribed deferasirox, and to monitor for signs and symptoms which could be suggestive of pancreatitis, such as abdominal pain, nausea, vomiting or tenderness of the abdomen to touch, particularly in paediatric patients.

In Hong Kong, there are three registered pharmaceutical products containing deferasirox, namely Exjade Dispersible Tab 125mg (HK-

54548), 250mg (HK-54547) and 500mg (HK-54549). All these products are prescription only medicines, and are registered by Novartis Pharmaceuticals (HK) Limited. In view of the HSA announcement, DH issued a letter to inform local healthcare professionals on 11 January 2016, and the matter will be discussed by the Registration Committee of the Pharmacy and Poisons Board. As on 10 March 2016, DH has received one ADR case in relation to deferasirox, but it was not related to acute pancreatitis.

## Singapore: Possible Fanconi Syndrome associated with zoledronic acid

It was noted from the HSA website on 11 January 2016 that HSA has received its first ADR report in Singapore of possible Fanconi Syndrome (FS) associated with zoledronic acid in August 2015. The patient presented with multiple electrolyte imbalances, together with low uric acid levels and mild proteinuria approximately 10 days after receiving a single intravenous (IV) infusion of zoledronic acid 4mg for bone metastases secondary to prostate cancer. At the time of reporting, the outcome was unresolved, with the patient still requiring oral calcium replacement therapy. Several cases of zoledronic acid-induced FS have been reported in the literature. Details of the ADR case report and literature reports can be found at the HSA website.

Zoledronic acid (Zometa®, Novartis (Singapore) Pte Ltd) has been registered in Singapore as a 4mg infusion since February 2005 for the treatment of osteolytic, osteoblastic, and mixed bone metastases of solid tumours and osteolytic lesions of multiple myeloma in conjunction with standard antineoplastic therapy, as well as for the treatment of hypercalcaemia of malignancy. There are also two other generic brands. Another strength (5mg infusion) of zoledronic acid (Aclasta®, Novartis (Singapore) Pte Ltd) has been registered in Singapore since March 2006 for the treatment of osteoporosis in post-menopausal women and in men at increased risk of fracture, prevention of glucocorticoid-induced bone mineral density loss, prevention of osteoporosis in post-menopausal women with increased risk of osteoporosis, and treatment of Paget's disease of the bone.

The diagnosis of drug-induced FS is usually suggested by a temporal relationship with exposure to a drug known to be toxic to the renal proximal tubule. However, it is worthwhile to note that with certain drugs such as tenofovir, toxicity can occur months or even years after establishing patients on treatment.

This is the first report of zoledronic acid-induced FS reported in Singapore. Healthcare professionals are advised to closely monitor the renal function of patients prescribed zoledronic acid so as to avoid the potential nephrotoxicity of the drug. Although some risk factors (i.e. elderly or very young population, pre-existing renal impairment and volume depletion) for drug-induced FS have been identified, in many cases it is unclear why patients develop toxicity while others do not. Pharmacogenomics has also been postulated to play a role in the development of drug-induced FS, although more research is required to establish this role.

In Hong Kong, there are 12 registered pharmaceutical products containing zoledronic acid, and are prescription only medicines. As on 10 March 2016, DH has not received any ADR case related to zoledronic acid. DH will continue to remain vigilant on the safety of medicines containing zoledronic acid.

## EU: EMA advice on use of colistin in animals to be updated: EMA acts upon request from European Commission following detection of colistin-resistant bacteria

On 11 January 2016, the European Medicines Agency (EMA) announced that they have received a request from the European Commission to update its advice on the use in animals of colistin, which is one of the last-resort antibiotics to treat certain bacterial infections in humans. This follows the recent discovery of a gene (called mcr-1) that causes bacteria to become resistant to colistin, an antibiotic of the polymyxin class that can easily be transferred between different types of bacteria. The gene was first detected in bacteria (called Enterobacteriaceae) that were isolated from pigs, pork and chicken products and from a small number of humans in South China. Since the gene was first detected it has subsequently been found

also in the European Union (EU).

Colistin or colistimethate sodium has been used for over 50 years in both humans and animals. In human medicines it is now used as a last resort medicine for the treatment of people suffering from different kinds of infections caused by multidrug-resistant bacteria. Because of its important role as a last defence against antimicrobial resistant bacteria, the EMA will consider if its 2013 advice on the responsible use of colistin in animals, particularly pigs, needs to be updated in light of the recent discovery.

To undertake this work, EMA's Committee for Veterinary Medicinal Products (CVMP) requested to reconvene the Antimicrobial Advice Ad Hoc Expert Group (AMEG), who prepared the 2013 advice.

The 2013 advice recommended maintaining the use of colistin in veterinary medicine but only for the treatment of infected animals and those in contact with them, and removing all indications for preventive (or prophylactic) use, in line with the principles of responsible use. It also recommended strengthening the systems for surveillance of antimicrobial resistance to colistin and carrying out a new review in case of a substantial increase of colistin resistance in animal bacteria or other new relevant information with a potential impact for public health.

AMEG will evaluate all available information and assess whether in the light of new evidence there is any impact on the 2013 advice for the use of colistin in animals within the EU. The update will take into account the importance of colistin to human and veterinary medicine, the impact of resistance, the availability of alternative treatments and the effectiveness of possible risk management measures for the protection of public and animal health in Europe.

The conclusions of the AMEG will be submitted to the CVMP and the CHMP for review and formal adoption before the updated advice is submitted to the European Commission. The EMA expects to finalise the update over the next six months.

In Hong Kong, there are three registered pharmaceutical products containing colistin or colistimethate sodium, namely Multibio Suspension Inj (Vet) (HK-42135), Colomycin for Inj 1 Million IU (HK-58514) and Colistin Powder for Solution for Injection 150mg (HK-63662). All these products are prescription only medicines. Multibio Suspension Inj (Vet) (HK-42135) is a multiple ingredients preparation containing colistin sulfate indicated for use in various animals including pigs.

EMA's 2013 advice on the responsible use of colistin in animals was previously reported in the Drug News Issue No. 45. DH issued a letter to inform local healthcare professionals on 31 July 2013. In 2014, the Registration Committee of the Pharmacy and Poisons Board decided that indications for preventive (or prophylactic) use of colistin should not be approved in new applications for registration of pharmaceutical products. As on 10 March 2016, DH has not received any ADR case on colistin and/or colistimethate sodium. In view of the start of evaluation by the AMEG, DH will remain vigilant on the conclusions and safety updates of colistin-containing medicines by other overseas drug regulatory authorities.

## Canada: TARCEVA (erlotinib) - Use in maintenance treatment for patients

On 21 January 2016, Health Canada announced that the benefit-risk of TARCEVA as maintenance treatment in patients with advanced non-small cell lung cancer (NSCLC) whose tumours do not have an epidermal growth factor receptor (EGFR) activating mutation is not considered favourable. TARCEVA is not effective for maintenance treatment in patients with locally advanced or metastatic NSCLC whose tumours do not have an EGFR activating mutation. The Canadian prescribing and consumer information for TARCEVA will be updated to reflect the new data.

TARCEVA (erlotinib) is a Human Epidermal Growth Factor Receptor Type 1/Epidermal Growth Factor Receptor (HER1/EGFR) tyrosine kinase inhibitor. It is currently indicated in patients with locally advanced or metastatic NSCLC:

- After failure of at least one prior chemotherapy regimen, and whose EGFR expression status by immunohistochemistry (IHC) is positive or unknown;
- As maintenance treatment in patients with

stable disease after 4 cycles of standard platinum-based first-line chemotherapy; no survival benefit is demonstrated in patients with EGFR-IHC negative or indeterminate tumours;
- As first-line treatment in patients with EGFR activating mutations.

The IUNO study (BO25460; NCT01328951) is a randomized, double-blind, placebo-controlled, phase 3 study of maintenance TARCEVA versus TARCEVA at the time of disease progression in patients with advanced NSCLC whose tumours did not harbor an EGFR-activating mutation (exon 19 deletion or exon 21 L858R mutation) and who have not progressed following 4 cycles of platinum-based chemotherapy. Details of the study can be found at the Health Canada website.

Based on the results observed in the IUNO study, the benefit-risk of TARCEVA is negative for maintenance treatment in patients whose tumours do not have an EGFR activating mutation. The study was not designed to demonstrate efficacy in patients whose tumours do have an EGFR activating mutation. Health Canada will be reviewing the maintenance indication.

Health care professionals are advised that the benefit-risk of TARCEVA is negative in the maintenance setting in patients with locally advanced or metastatic NSCLC whose tumours do not have an EGFR activating mutation. The role of Tarceva as maintenance therapy in patients whose tumours harbor an EGFR activating mutation (exon 19 deletion or exon 21 L858R mutation) with locally advanced or metastatic NSCLC will be assessed by Health Canada.

In Hong Kong, there are six registered pharmaceutical products containing erlotinib, namely Tarceva Tab 25mg (HK-54114), Tarceva Tab 100mg (HK-54113), Tarceva Tab 150mg (HK-54112), Tarceva Tab 25mg (Italy) (HK-57441), Tarceva Tab 100mg (Italy) (HK-57440) and Tarceva Tab 150mg (Italy) (HK-57439). All these products are prescription only medicines, and are registered by Roche Hong Kong Limited (Roche HK).

On 22 January 2016, Roche HK notified DH that the company would issue a "Dear Healthcare Professional Letter" to relevant oncologists, pulmonologists and pharmacists to draw their attention on study observation. As on 10 March 2016, DH has received five ADR cases in relation to erlotinib, and two of them were related to disease progression. In view of the above announcement, the matter will be discussed by the Registration Committee of the Pharmacy and Poisons Board. DH will continue to remain vigilant on the safety of medicines containing erlotinib.

## EU: Review of metformin-containing medicines started

On 29 January 2016, the EMA has started a review of all metformin-containing medicines. Metformin, alone or in combination with other medicines, is widely used for treating type 2 diabetes.

This review was requested by the Dutch medicines agency (the Medicines Evaluation Board, MEB) following a routine evaluation of the safety of metformin medicines. This evaluation showed that the prescribing information for metformin-containing medicines varies between countries and products in its advice on how the medicine should be used in patients with reduced kidney function. Metformin may cause a rare but serious complication called lactic acidosis, which is when lactic acid, a natural by-product of the body, builds up in the blood faster than it can be removed. Patients on metformin who have significant reduction in kidney function are at a higher risk of developing lactic acidosis because their kidneys are unable to remove enough lactic acid. Thus, currently the prescribing information states that metformin must not be used in these patients.

The Dutch review found that the current scientific evidence might not justify contraindicating metformin in patients with moderate reduction of kidney function. This large group of patients may stand to benefit from treatment with metformin. In addition, the recommendations in the prescribing information are often inconsistent with clinical guidelines on the treatment of diabetes. Thus, the

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MEB considered that the prescribing information for all metformin-containing medicines should be reviewed to harmonise the recommendations on their use in patients with significant kidney problems.

EMA will now review the data on the different metformin medicines and consider how the prescribing information for these medicines should be updated, and it will issue an opinion on the marketing authorisations of these medicines across the EU.

In Hong Kong, there are 120 registered pharmaceutical products containing metformin, which are prescription only medicines. As on 10 March 2016, the DH has received seven ADR cases in relation to metformin, and two of them involved lactic acidosis after taking the drug. As Martindale has stated biguanides (including metformin) are generally avoided in patients with renal impairment because of the risk of lactic acidosis, and the EMA has just started the review of metformin-containing medicines which has not yet concluded, DH will remain vigilant on the conclusion of the review and safety updates from other overseas drug regulatory authorities.

# Drug Incident

**Man arrested for suspected illegal sale of unregistered pharmaceutical product**

On 27 January 2016, a man aged 20 was arrested in a joint operation by DH and the Police for suspected illegal sale of an unregistered pharmaceutical product.

Acting upon a public complaint, it was found that a patch labelled in Japanese as containing a Part 1 poison, felbinac, was being offered for sale via the Internet. No Hong Kong pharmaceutical registration number was found on the product label.

Felbinac is a non-steroidal anti-inflammatory drug used topically to relieve pain. Inappropriate use may cause erythema and dermatitis.

People who have purchased the above product should stop using it and consult healthcare professionals for advice if they feel unwell. A notice was released on the website of the Drug Office on the same day to alert the public of the drug incident.

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.***