



This is a monthly digest of local and overseas drug safety news released by the Drug Office of the Department of Health in May 2019 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: Restrictions in use of Xeljanz while EMA reviews risk of blood clots in lungs

On 17 May 2019, the European Medicines Agency (EMA) of the European Union (EU) announced that the EMA's safety committee, the Pharmacovigilance Risk Assessment Committee (PRAC), is recommending that doctors must not prescribe the 10 mg twice daily dose of Xeljanz (tofacitinib) in patients who are at high risk of blood clots in the lungs. These include patients who have heart failure, cancer, inherited blood clotting disorders or a history of blood clots, as well as patients who take combined hormonal contraceptives, are receiving hormone replacement therapy or are undergoing major surgery.

In addition, doctors should consider other factors that may increase the risk of blood clots in the lungs including age, obesity, smoking or immobilisation.

Xeljanz is currently authorised for the treatment of rheumatoid arthritis, psoriatic arthritis and severe ulcerative colitis in the EU.

The PRAC's recommendation follows results from an ongoing study (study A3921133) in patients with rheumatoid arthritis. This study showed an increased risk of blood clots in the lungs and death when the 10 mg twice daily dose was used, which is double the recommended dose for rheumatoid arthritis.

The new advice means that, since 10 mg is the only recommended starting dose for ulcerative colitis, patients with this condition who are at high risk of blood clots must not be started on Xeljanz. Patients at high risk currently taking this dose for any

condition must be switched to alternative treatments.

Patients are advised that they should not stop or change their dose of Xeljanz without talking to their doctor. They should seek medical attention immediately if they experience symptoms such as difficulty breathing, pain in the chest or upper back and coughing up blood, which could indicate the presence of a blood clot in the lungs.

The new recommendations are temporary and follow previous PRAC advice not to exceed the recommended 5 mg twice daily dose when treating rheumatoid arthritis. The PRAC will now carry out a review of all available evidence, and updated guidance will be provided to patients and healthcare professionals once the review is concluded.

Information for patients

- An ongoing study in patients with rheumatoid arthritis showed that when Xeljanz was given at a dose of 10 mg twice daily there was an increased risk of dangerous blood clots in the lungs and death.
- This dose is higher than the approved dose of 5 mg twice daily for rheumatoid arthritis. However, this dose is used for the initial treatment of patients with ulcerative colitis (for up to 16 weeks) and may also be used in some patients when continuing treatment.
- While an in-depth review of Xeljanz is ongoing, if patients are being treated with Xeljanz 10 mg twice daily and they are at high risk of blood clots in the lungs, their doctor may switch them to an alternative treatment.
- They may be at high risk of blood clots in the lungs if they:

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- have heart failure (when the heart does not work as well as it should)
 - have inherited blood clotting disorders
 - have had blood clots in the veins
 - are taking combined hormonal contraceptives or hormone replacement therapy
 - have cancer
 - will have or have recently had major surgery.
 - Their doctor will also take into account their age, whether they are obese (their body mass index is above 30), smoke or are immobilised when evaluating their risk of blood clots.
 - If they are being treated with Xeljanz, they should not change the dose or stop taking the medicine without discussing it with their doctor.
 - They should seek medical attention immediately if they experience the following symptoms which may be signs of a blood clot in their lungs: difficulty breathing, chest pain or pain in their upper back, coughing up blood, excessive sweating and bluish skin.
 - If they have any concerns about their medicine, they should discuss them with a healthcare professional.
- Information for healthcare professionals
- An increased risk of pulmonary embolism and overall mortality has been observed in a study with tofacitinib 10 mg twice daily in rheumatoid arthritis.
 - These results come from study A3921133, an ongoing open-label clinical trial evaluating the safety of tofacitinib 5 mg twice daily and tofacitinib 10 mg twice daily compared with a tumour necrosis factor (TNF) inhibitor in patients with rheumatoid arthritis. Patients in the study are 50 years of age or older with at least one additional cardiovascular risk factor.
 - The preliminary results of the study showed that there were 19 cases of pulmonary embolism out of 3,884 patient-years in the tofacitinib 10 mg twice daily arm of the study compared with 3 cases out of 3,982 in the TNF inhibitor arm. Additionally, there were 45 deaths from all causes out of 3,884 patient-years in the 10 mg twice daily arm compared with 25 cases out of 3,982 patient-years in the TNF inhibitor group.
- While an in-depth review of these risks is ongoing, doctors must not prescribe the 10 mg twice daily dose in patients:
 - with heart failure
 - with inherited coagulation disorders
 - who have had venous thromboembolism, either deep venous thrombosis or pulmonary embolism
 - who use combined hormonal contraceptives or hormone replacement therapy
 - with malignancy
 - who are undergoing major surgery.
 - Additionally, other risk factors to be considered when prescribing tofacitinib 10 mg twice daily include age, obesity (Body Mass Index [BMI]>30), smoking and immobilisation.
 - Patients who are already treated with the 10 mg twice daily dose and are at high risk of pulmonary embolism should be switched to alternative treatments.
 - While further assessment of the study results continues, prescribers should continue to adhere to the authorised dose of 5 mg twice daily for the treatment of rheumatoid arthritis and psoriatic arthritis.
 - Patients receiving tofacitinib, irrespective of indication, should be monitored for the signs and symptoms of pulmonary embolism, and be advised to seek medical attention immediately if they experience them.
 - A letter is being sent to all healthcare professionals expected to prescribe the medicine to inform them of the temporary treatment recommendations.

In Hong Kong, Xeljanz Tablets 5mg (HK-63303) and Xeljanz XR Extended Release Tablets 11mg (HK-66141) are registered pharmaceutical products containing tofacitinib. Both products are registered by Pfizer Corporation Hong Kong Limited, and are prescription-only medicines. As of 5 June 2019, the Department of Health (DH) has received 3 cases of adverse drug reaction (ADR) related to tofacitinib, but these cases are not related to blood clots in the lungs. Related news was previously issued by the United States (US) Food and Drug Administration (FDA), Health Canada, the EMA and the Therapeutic Goods Administration (TGA), and was reported in the Drug News Issue No. 112. As the

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clinical trial is ongoing, the DH will remain vigilant on the results of the trial and safety update of the drug issued by various overseas drug regulatory authorities for consideration of any action deemed necessary.

UK: Magnesium sulfate: risk of skeletal adverse effects in the neonate following prolonged or repeated use in pregnancy

On 17 May 2019, the Medicines and Healthcare products Regulatory Agency (MHRA) of the United Kingdom (UK) announced that maternal administration of magnesium sulfate for longer than 5–7 days in pregnancy has been associated with skeletal adverse effects and hypocalcaemia and hypermagnesaemia in neonates. If use of magnesium sulfate in pregnancy is prolonged or repeated, consider monitoring of neonates for abnormal calcium and magnesium levels and skeletal adverse effects.

The MHRA is not aware of any reports in the UK of skeletal adverse effects or relevant biochemical effects in the neonate following use of magnesium sulfate for foetal neuroprotection. However, following efforts to achieve increased uptake in preterm labour and birth (including through the PReCePT project), data suggests usage is increasing in the UK. Healthcare professionals should therefore be vigilant for any adverse effects in the neonatal period if in-utero exposure to magnesium sulfate is prolonged.

The Commission on Human Medicines and its Expert Advisory Groups, the Medicines for Women's Health Expert Advisory Group, and the Paediatric Medicines Expert Advisory Group considered data for the use of magnesium sulfate in the UK. Based on their recommendations, the product information for products containing magnesium sulfate in the UK will be updated to warn of skeletal adverse effects observed with administration for more than 5–7 days in pregnancy.

Healthcare professionals are advised of the followings:

- Maternal administration of magnesium sulfate

for longer than 5–7 days in pregnancy may be associated with adverse effects in the foetus, including hypocalcaemia, skeletal demineralisation, osteopenia, and other skeletal adverse effects.

- If prolonged or repeated use of magnesium sulfate occurs during pregnancy (for example, multiple courses or use for more than 24 hours), consider monitoring of neonates for abnormal calcium and magnesium levels and skeletal adverse effects.
- Report suspected ADRs to magnesium sulfate following exposure during pregnancy on a Yellow Card.

In Hong Kong, there are three registered injectable pharmaceutical products containing magnesium sulfate, which are indicated for the treatment and prevention of hypomagnesaemia, pre-eclampsia and eclampsia and are prescription-only medicines. As of 5 June 2019, the DH has not received any adverse reaction report related to the drug.

Related news regarding recommendation against prolonged use of magnesium sulfate in pregnancy was previously released by the US FDA, and was reported in the Drug News Issue No. 43. The DH issued a letter to inform local healthcare professionals to draw their attention on the warnings on 31 May 2013. The matter has been discussed in the meeting of the Registration Committee of the Pharmacy and Poisons Board (Registration Committee) on 3 December 2014. The Registration Committee decided that the product inserts of injectable pharmaceutical products containing magnesium sulfate should be updated to include the relevant safety information. The package inserts for all the above three registered injectable pharmaceutical products containing magnesium sulfate have been updated to include the above safety information endorsed by the Registration Committee. The DH will remain vigilant on any further safety update of the drug issued by other overseas drug regulatory authorities.

Canada: Important safety information on ACTEMRA (tocilizumab) - Risk of hepatotoxicity

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On 21 May 2019, Health Canada announced that serious cases of drug-induced liver injuries (DILI) have been reported in patients treated with ACTEMRA, including cases of acute liver failure requiring a transplant. There have been cases of serious liver injury reported from Canada.

ACTEMRA is known to cause transient or intermittent mild to moderate elevation of hepatic transaminases. This risk is increased when ACTEMRA is used in combination with potentially hepatotoxic drugs (e.g., methotrexate).

Following Health Canada's request, the Market Authorization Holder performed a cumulative, comprehensive assessment of serious hepatic injury including hepatic failure reported with ACTEMRA across all available clinical and post-marketing data sources, including data from the Food and Drug Administration Adverse Event Reporting System (FAERS) and Eudravigilance (EV) databases and from the literature. Eight cases of ACTEMRA-related moderate to severe DILI were identified. These events occurred between 2 weeks to more than 5 years after initiation of tocilizumab with median latency of 98 days. Two of these 8 cases required liver transplantation. The total world-wide ACTEMRA exposure is estimated to be 1,066,849 patients (corresponding to 882,370.3 Patient Years) up to 10 April 2018.

Consumers are advised:

- In some patients, ACTEMRA has been associated with drug-induced liver injuries, which can be serious, life-threatening or even fatal.
- Before taking ACTEMRA, patients or their caregivers should talk to their healthcare professional if they have, or have had, liver problems. Before and/or during treatment, patients should have blood tests done to check their liver function.
- If patients experience signs of liver injury such as loss of appetite, nausea and vomiting, fatigue, itching, dark urine, yellowing of skin and eyes, abdominal swelling, and/or pain in the upper-right abdomen, they or their caregivers should speak with their healthcare professional. Patients receiving ACTEMRA should also inform their healthcare professional if they experience any adverse

effects.

Healthcare professionals are advised:

- Not recommend ACTEMRA in patients with active hepatic disease or hepatic impairment.
- Not initiate treatment with ACTEMRA in patients with elevated blood liver enzyme levels above 3 times the upper limit of normal (ULN).
- Discontinue treatment with ACTEMRA in patients with elevated blood liver enzyme levels above 5 times the ULN.
- Exercise caution when considering starting ACTEMRA treatment in patients with liver enzyme levels above 1.5 times the ULN.
- Monitor liver function tests (LFTs) in patients with rheumatoid arthritis and giant cell arteritis every 4 to 8 weeks for the first 6 months of treatment, followed by every 12 weeks thereafter.
- Monitor LFTs in patients with polyarticular juvenile idiopathic arthritis and systemic juvenile idiopathic arthritis before treatment begins, at the time of the second ACTEMRA treatment, and every 2 to 4 weeks thereafter.
- Refer to the approved Canadian Product Monograph for guidance on the recommended dose adjustments (reduction, interruption or discontinuation) in patients with liver enzyme elevations.
- Advise patients to contact a healthcare professional if they experience signs of liver injury such as loss of appetite, nausea and vomiting, fatigue, itching, dark urine, yellowing of skin and eyes, abdominal swelling and/or pain in the upper-right abdomen.

Health Canada is working with the manufacturer to include this new safety information in the Canadian Product Monograph.

In Hong Kong, there are 4 registered pharmaceutical products containing tocilizumab, namely Actemra Conc for Soln for Infusion 400mg/20ml (HK-59200), Actemra Conc for Solution for Inf 200mg/10ml (HK-59201), Actemra Conc for Soln for Infusion 80mg/4ml (HK-59202) and Actemra Solution for Injection in Pre-filled Syringe 162mg/0.9ml (HK-63771). All products are registered by Roche Hong Kong Limited, and

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are prescription-only medicines. As of 5 June 2019, the DH has received 8 cases of ADR related to ticilizumab, but these cases are not related to hepatotoxicity. Related news was previously issued by Singapore Health Sciences Authority (HSA), and was reported in the Drug News Issue No. 114. The DH issued a letter to inform local healthcare professionals to draw their attention on 12 April 2019. In light of the above Health Canada's announcement, the matter will be discussed by the Registration Committee.

EU: Withdrawal of marketing authorisations for fenspiride medicines

On 29 May 2019, the EMA announced that the PRAC recommended on 16 May 2019 that the marketing authorisations for fenspiride medicines be revoked, so the medicines can no longer be marketed in the EU. This follows a review that confirmed that these cough medicines could cause heart rhythm problems. The PRAC considered all the available evidence in its review. This included cases of QT prolongation and torsades de pointes (abnormalities of the heart's electrical activity that may lead to heart rhythm disturbances) in patients using these medicines, results of laboratory studies, data from published literature and stakeholder input. Heart rhythm problems can be serious and occur suddenly, and it is not feasible to identify in advance the patients who may be at risk of these problems with fenspiride. In contrast, fenspiride medicines are used to treat non-serious cough. Therefore, the PRAC considered that these medicines should no longer be marketed.

The PRAC recommendation was adopted by the Co-ordination Group for Mutual Recognition and Decentralised Procedures – Human (CMDh) by consensus on 29 May 2019 and will be implemented directly at national level.

Information for patients:

- Cough medicines containing fenspiride will no longer be marketed in the EU because of data showing a risk of sudden, serious heart rhythm problems.
- Patients should stop taking these medicines and contact their doctor or pharmacist for advice on alternative treatments, if needed.

They can check the ingredients of their medicine in the package leaflet accompanying the medicine.

- Patients are only at risk of heart rhythm problems with fenspiride while they are taking these medicines.
- If they have any concerns about their medicine, discuss them with their doctor or pharmacist.
- Return unused medicines to their pharmacy for appropriate disposal.

Information for healthcare professionals:

- Healthcare professionals should no longer prescribe fenspiride medicines and should advise their patients to stop taking fenspiride medicines.
- The withdrawal of the marketing authorisations of fenspiride medicines is based on case reports and nonclinical studies (including hERG channel binding) that showed that fenspiride can cause QT prolongation and has proarrhythmia potential (could cause triggering or worsening of arrhythmia) with the associated risk of torsades de pointes.
- Given the authorised uses of fenspiride for symptomatic treatment only and the seriousness of the safety concern, the benefit-risk balance of these medicines is negative for the currently authorised uses.

In Hong Kong, there is one registered pharmaceutical product containing fenspiride, namely Fenspiride Tab 40mg "P.L." (HK-59766). The product is registered by Julius Chen & Co (HK) Ltd, and is classified as a non-poison. As of 5 June 2019, the DH has not received any case of ADR related to fenspiride. Related news was previously issued by the EMA, and was reported in the Drug News Issue No. 112. The DH issued a letter to inform local healthcare professionals to draw their attention on 18 February 2019. In light of the above EMA's announcement, the matter will be discussed by the Registration Committee.

Advice to Health Professionals

Legal requirements on handling of pharmaceutical products by healthcare professionals

In view of the recent reports relating to suspected unregistered vaccines being supplied by local clinics, the DH issued a letter to healthcare professionals to reiterate the legal requirements on drug handling on 30 May 2019.

Legal requirements on drug handling by registered medical practitioners and dentists

In Hong Kong, the principle Ordinance that governs pharmaceutical products is the Pharmacy and Poisons Ordinance (Cap. 138) ("PPO") and its subsidiary regulations, in particular the Pharmacy and Poisons Regulations (Cap. 138A) ("PPR").

According to section 28 of the PPO, a registered medical practitioner may supply a medicine for the purposes of medical treatment, and a registered dentist may supply a medicine for the purposes of dental treatment as long as the provisions in section 28 are satisfied. These include:

- The medicine shall be distinctly labeled with the name and address of the medical practitioner or dentist who supply the medicine (section 28(2)).
- The registered medical practitioner or dentist must enter in the record of treatment or other document:
 - (a) the date on which the medicine was supplied;
 - (b) the name and address of the patient; and
 - (c) the ingredients of the medicine and the quantity, dosage and duration of supply (section 28(3A)).

Nevertheless, other requirements stipulated under the PPR still apply to registered medical practitioners or dentists. These include, inter alia, wholesale dealing of pharmaceutical products requires licence (Part 6 of the PPR), manufacture of pharmaceutical products requires licence (except dispensing of medicine for individual patient treatment) (Part 7 of the PPR), and all pharmaceutical products must be registered with the Pharmacy and Poisons Board before sale and supply (Part 8 of the PPR).

In addition, other Ordinances may be relevant to healthcare professionals when handling drugs. These include, but not limited to, the Antibiotics Ordinance (Cap. 137), the Dangerous Drugs Ordinance (Cap. 134), the Import and Export Ordinance (Cap. 60) and the Public Health and Municipal Services Ordinance (Cap. 132). For details of the provisions, please refer to respective Ordinances which could be downloaded at www.elegislation.gov.hk. For easy reference, a summary of offences that are relevant to registered medical practitioners and dentists is listed below.

Summary of drug-related offences relevant to healthcare professionals

Provision	Offence	Maximum Penalty	Remarks
Sec 28 of PPO	Improper labelling or fail to keep proper record by registered medical practitioner or registered dentist	\$100,000 fine and 2 years imprisonment	
Reg 25 of PPR	Illegal sale of pharmaceutical products by way of wholesale dealing		
Reg 29 of PPR	Manufacture pharmaceutical products without licence		Manufacture does not include individual dispensing
Reg 36 of PPR	Sale or possession for sale of unregistered pharmaceutical products		A medical practitioner or dentist may possess or use an unregistered pharmaceutical product for the purpose of treatment of a particular patient
Sec 7 of ABO	Fail to keep proper record of antibiotics	\$5,000 fine	

Advice to Health Professionals

Sec 4 of DDO	Trafficking in dangerous drug	\$5,000,000 fine and life imprisonment	Registered medical practitioners are authorized to possess and supply certain dangerous drugs necessary for the practice of his profession
Sec 8 of DDO	Possession of dangerous drug	\$1,000,000 fine and 7 years imprisonment	Registered dentists are authorized to possess and administer certain dangerous drugs necessary for the practice of his profession
Reg 5 of DDR	Fail to keep dangerous drugs register	\$450,000 fine and 3 years imprisonment	
Reg 7 of DDR	Fail to preserve documents	\$10,000 fine and 12 months imprisonment	
Sec 52 of PHMSO	Sell to a purchaser a drug not of the nature, substance or quality demanded by the purchaser	\$10,000 fine and 3 months imprisonment	
Sec 61 of PHMSO	Sell a drug with a label falsely describes the drug or is calculated to mislead as to its nature, substance or quality	\$50,000 fine and 6 months imprisonment	
Sec 6C & 6D of IEO	Import or export a medicine not under and in accordance with an import licence or export licence	\$500,000 fine and 2 years imprisonment	

Notes:

- 1} The above list only highlights most common drug-related offences that are relevant to healthcare professionals and it is not an exhaustive list.
- 2} Abbreviations for the Ordinances:
 - PPO: Pharmacy and Poisons Ordinance, Cap. 138
 - PPR: Pharmacy and Poisons Regulations, Cap. 138A
 - ABO: Antibiotics Ordinance, Cap. 137
 - DDO: Dangerous Drugs Ordinance, Cap. 134
 - DDR: Dangerous Drugs Regulations, Cap. 134A
 - PHMSO: Public Health and Municipal Services Ordinance, Cap. 132
 - IEO: Import and Export Ordinance, Cap. 60

Other advice on drug handling by healthcare professionals

To assure pharmaceutical products are supplied from legitimate source and under proper logistic management, healthcare professionals are advised to only procure and obtain pharmaceutical products from licensed wholesale dealers, licensed manufacturers or authorized sellers of poisons (regulation 25 of PPR). The pharmaceutical products supplied by these licensed dealers should also be registered with the Pharmacy and Poisons Board in accordance with regulation 36 of the PPR. Information on registered pharmaceutical products and licensed dealers is available at the Drug Office's website (www.drugoffice.gov.hk).

Upon receipt of the medicines from licensed suppliers, healthcare professionals are advised to check and verify the delivery and to keep proper storage of the medicines received, especially those require special storage conditions, e.g. vaccines at 2 -8°C. For storage of vaccines, a purpose-built vaccine refrigerator is the preferred mean but domestic frost-free refrigerator may be used if proper measures and precautions are in place. For more information, please refer to Section 3.3 of the Guide: https://www.pco.gov.hk/english/resource/files/Module_on_Immunisation_Children.pdf.

Advice to Health Professionals

Should healthcare professionals suspect any person supplying unregistered pharmaceutical products or supply a pharmaceutical product without licence,

they may provide such information to the Drug Office of the DH (Tel: 2572 2068; Email: pharmgeneral@dh.gov.hk) for further action.

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.

Under the Import and Export Ordinance (Cap. 60), pharmaceutical products must be imported or exported under and in accordance with an import or export licence issued under the Import and Export Ordinance. Illegal import or export of pharmaceutical products are offences under the Import and Export Ordinance (Cap. 60) and the maximum penalty is a fine of \$500,000 and 2 years' imprisonment.

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

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.