Drug News
藥 物 情 報

Issue Number 78

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

US: FDA adds warnings about heart failure risk to labels of type 2 diabetes medicines containing saxagliptin and alogliptin

On 5 April 2016, a United States (U.S.) Food and Drug Administration (FDA) safety review has found that type 2 diabetes medicines containing saxagliptin and alogliptin may increase the risk of heart failure, particularly in patients who already have heart or kidney disease. This is an update to the FDA Drug Safety Communication: FDA to review heart failure risk with diabetes drug saxagliptin (marketed as Onglyza and Kombiglyze XR) issued on February 11, 2014. Heart failure can result in the heart not being able to pump enough blood to meet the body's needs. As a result, FDA is adding new Warnings and Precautions to the drug labels about this safety issue.

Saxagliptin and alogliptin are part of the class of dipeptidyl peptidase-4 (DPP-4) inhibitor drugs, which are used with diet and exercise to lower blood sugar in adults with type 2 diabetes. Untreated, type 2 diabetes can lead to serious health problems, including blindness, nerve and kidney damage, and heart disease. Saxagliptin is marketed as Onglyza and Kombiglyze XR, while alogliptin is marketed as Nesina, Kazano and Oseni in the U.S.

FDA evaluated two large clinical trials conducted in patients with heart disease. These clinical trials were also discussed at the FDA Endocrinologic and Metabolic Drugs Advisory Committee meeting in April 2015. Each trial showed that more patients who received saxagliptin- or alogliptin-containing medicines were hospitalized for heart failure compared to patients who received an inactive treatment called a placebo.

Patients are advised to contact their healthcare professional right away if they develop signs and symptoms of heart failure when taking saxagliptin or alogliptin, such as:

- Unusual shortness of breath during daily activities
- Trouble breathing when lying down
- Tiredness, weakness, or fatigue
- Weight gain with swelling in the ankles, feet, legs, or stomach

Healthcare professionals are advised of the following:

- Risk factors of hospitalization for heart failure include a history of heart failure or renal impairment, and this safety risk was found in clinical trials among patients with these medical issues.
- Consider the risk and benefits of saxagliptin or alogliptin prior to initiating treatment in patients at a higher risk for heart failure.
- Observe patients receiving saxagliptin or alogliptin for signs and symptoms of heart failure.
- Consider discontinuing the drug and monitor diabetes control if heart failure develops. If blood sugar level is not well-controlled with a patient's current treatment, other diabetes medicines may be required.
- Encourage patients to read the Medication Guide they receive with their prescriptions.

In Hong Kong, there are five registered pharmaceutical products containing saxagliptin approved under the brand names of Onglyza and Kombiglyze XR, and seven registered products

containing alogliptin approved under the brand names of Oseni and Nesina. All these products are prescription only medicines. Related news on review of heart failure of saxagliptin was previously issued by the FDA, and was reported in the Drug News Issue No. 52. The Department of Health (DH) issued a letter to inform local healthcare professionals on 12 Februrary 2014. As on 13 June 2016, DH has not received any adverse drug reaction (ADR) case related to saxagliptin or alogliptin. In view of the conclusion of the FDA safety review, DH issued a letter to inform local healthcare professionals on 6 April 2016, and the matter will be discussed by the Registration Committee of the Pharmacy and Poisons Board (the Registration Committee).

US: FDA revises warnings regarding use of the diabetes medicine metformin in certain patients with reduced kidney function

On 8 April 2016, the U.S. FDA is requiring labeling changes regarding the recommendations for metformin-containing medicines for diabetes to expand metformin's use in certain patients with reduced kidney function. The current labeling strongly recommends against use of metformin in some patients whose kidneys do not work normally. FDA was asked to review numerous medical studies regarding the safety of metformin use in patients with mild to moderate impairment in kidney function, and to change the measure of kidney function in the metformin drug labeling that is used to determine whether a patient can receive metformin.

FDA concluded, from the review of studies published in the medical literature, that metformin can be used safely in patients with mild impairment in kidney function and in some patients with moderate impairment in kidney function. FDA is requiring changes to the metformin labeling to reflect this new information and provide specific recommendations on the drug's use in patients with mild to moderate kidney impairment.

FDA is also requiring manufacturers to revise the labeling to recommend that the measure of kidney function used to determine whether a patient can receive metformin be changed from one based on a single laboratory parameter (blood creatinine concentration) to one that provides a better estimate of renal function (i.e., glomerular filtration rate estimating equation (eGFR)). This is because in addition to blood creatinine concentration, the glomerular filtration rate takes into account additional parameters that are important, such as the patient's age, gender, race and/or weight.

Healthcare professionals should follow the latest recommendations when prescribing metformin-containing medicines to patients with impaired kidney function. Patients should talk to their healthcare professionals if they have any questions or concerns about taking metformin.

The labeling recommendations on how and when kidney function is measured in patients receiving metformin will include the following information:

- Before starting metformin, obtain the patient's eGFR.
- Metformin is contraindicated in patients with an eGFR below 30 mL/minute/1.73 m^2.
- Starting metformin in patients with an eGFR between 30-45 mL/minute/1.73 m^2 is not recommended.
- Obtain an eGFR at least annually in all patients taking metformin. In patients at increased risk for the development of renal impairment such as the elderly, renal function should be assessed more frequently.
- In patients taking metformin whose eGFR later falls below 45 mL/minute/1.73 m^2, assess the benefits and risks of continuing treatment. Discontinue metformin if the patient's eGFR later falls below 30 mL/minute/1.73 m^2.
- Discontinue metformin at the time of or before an iodinated contrast imaging procedure in patients with an eGFR between 30 and 60 mL/minute/1.73 m^2; in patients with a history of liver disease, alcoholism, or heart failure; or in patients who will be administered intra-arterial iodinated contrast. Re-evaluate eGFR 48 hours after the imaging procedure; restart metformin if renal function is stable.

In Hong Kong, there are 121 registered pharmaceutical products containing metformin, which are prescription only medicines. Related news on starting a review of metformin-containing medicines by the European Medicines Agency (EMA), and was reported in the Drug News Issue No. 75. As on 13 June 2016, DH has received eight ADR cases related to metformin, and two of them

involved lactic acidosis after taking the drug. In view of the above FDA announcement, DH issued a letter to inform local healthcare professionals on 11 April 2016, and the matter will be discussed by the Registration Committee. DH will remain vigilant on the conclusion of the review by EMA and safety updates from other overseas drug regulatory authorities.

EU: EMA reviews diabetes medicine canagliflozin following data on toe amputations in ongoing study

On 15 April 2016, EMA has started a review of the diabetes medicine canagliflozin after an increase in amputations, mostly affecting toes, was observed in an ongoing clinical trial called CANVAS (CANagliflozin cardioVascular Assessment Study).

Canagliflozin is an SGLT2 inhibitor. It works by blocking a protein in the kidneys called sodium glucose co-transporter 2 (SGLT2). SGLT2 absorbs glucose back into the bloodstream as the blood is filtered in the kidneys. By blocking the action of SGLT2, canagliflozin causes more glucose to be removed via the urine, thereby reducing glucose in the blood. The other SGLT2 inhibitors are dapagliflozin and empagliflozin.

Cases of lower limb amputation occurred in both the canagliflozin and placebo groups in the trial and the possibility that canagliflozin increases lower limb amputations is currently not confirmed. EMA's Pharmacovigilance Risk Assessment Committee (PRAC) has requested more information from the company to assess whether canagliflozin causes an increase in lower limb amputations and whether any changes are needed in the way this medicine is used in the European Union (EU).

Patients with diabetes (especially those with poorly controlled diabetes and pre-existing problems with the heart and blood vessels) are at increased risk of infection and ulceration which can result in lower limb amputations. No increase in such amputations was seen in 12 other completed clinical trials with canagliflozin. A small, non-statistically significant increase in the number of amputations occurred in another ongoing study called CANVAS-R. Both CANVAS and CANVAS-R involve patients at high risk of problems with the heart and blood vessels.

The PRAC will also ask for data on other medicines in the same class known as SGLT2 inhibitors. Based on this, the PRAC may decide to extend the scope of the review to cover these medicines.

While the review on canagliflozin is ongoing, healthcare professionals in the EU will receive a letter reminding them about the importance of routine foot care to avoid cuts or sores of the feet and to treat them promptly should they occur to prevent infection and ulceration. Patients at increased risk of amputation (such as those who have had a previous amputation) should be carefully monitored. As a precautionary measure, doctors may consider stopping treatment with canagliflozin in patients who develop significant foot complications.

In Hong Kong, there are two registered pharmaceutical products containing canagliflozin, namely Invokana Tablets 100mg (HK-63499) and Invokana Tablets 300mg (HK-63500) which are registered by Johnson & Johnson (HK) Ltd, and are prescription only medicines. According to our record, there is no application for clinical trial certificates for CANVAS and CANVAS-R in Hong Kong. As on 13 June 2016, DH has received one case of ADR in connection with canagliflozin, but it was not related to amputation. Since letters to healthcare professionals reminding them about the importance of routine foot care will be issued by EMA while the review on canagliflozin is ongoing, DH issued a letter to inform local healthcare professionals to draw their attention. DH will remain vigilant on the conclusion of the review and any safety updates from other overseas drug regulatory authorities.

EU: EMA reviews direct-acting antivirals for hepatitis C (interferon-free) - extension of scope of review

On 15 April 2016, EMA announced extension of scope of review on direct-acting antivirals for hepatitis C (interferon-free). On 17 March 2016, EMA started 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).

Direct-acting antivirals (Daklinza, Exviera, Harvoni, Olysio, Sovaldi and Viekirax in EU) 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 was triggered by reports 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. The review will 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.

In addition, in April 2016 data from a study became available regarding the risk of liver cancer (hepatocellular carcinoma) coming back in patients who were treated with direct-acting antivirals for hepatitis C. The study suggested that these patients were at risk of their cancer coming back earlier than patients with hepatitis C who were not treated with direct-acting antivirals. The scope of the ongoing review has therefore been extended to also assess the risk of liver cancer with these medicines. 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)] and Sovaldi Tablets 400mg [sofosbuvir (HK-63501)] are pharmaceutical products registered by Gilead Sciences Hong Kong Limited, while Viekira Pak Tablets [ombitasvir/ paritaprevir/ ritonavir/ dasabuvir (HK-63695)] is a pharmaceutical product registered by Abbvie Limited. All these products are prescription only medicines. There is no registered pharmaceutical product containing daclatasvir or simeprevir. Related news on review to assess the extent of hepatitis B re-activation was issued by EMA, and was reported in the Drug News Issue No. 77. As on 13 June 2016, DH has received two cases and eleven cases of ADR in connection with Sovaldi and Viekira Pak respectively, but none of them was related to hepatitis B re-activation or liver cancer. In view of the extension of scope of EMA review to include liver cancer, DH issued a letter to inform local healthcare professionals on 18 April 2016 to draw their attention. DH will remain vigilant on the conclusion of the review and any safety updates from other overseas drug regulatory authorities.

UK: Live attenuated vaccines: avoid use in those who are clinically immunosuppressed

On 18 April 2016, the Medicines and Healthcare products Regulatory Agency (MHRA) of UK (the United Kingdom) advised that healthcare professionals working in primary and secondary care should ensure that clinically significant immunosuppression in a patient is identified before administration of a live attenuated vaccine. Use of live attenuated vaccines should be avoided in these patients.

Some recommended vaccines contain live, attenuated (weakened) organisms, which work by mimicking a natural infection. Live attenuated vaccines should not be given to people who are clinically immunosuppressed (either due to drug treatment or underlying illness) because the vaccine strain could replicate too much and cause an extensive, serious infection. A minor immunodeficiency may not necessarily contraindicate vaccination.

The MHRA is aware of recent Yellow Card adverse reaction reports in which immunosuppressed patients have received a live attenuated vaccine, some of which resulted in severe infection and death, including the following:

1) Fatal BCG infection in neonates after in utero exposure to TNFα antagonist
   The MHRA has received 4 Yellow Card reports regarding neonates who have died from disseminated BCG or tuberculosis infection after exposure to a TNFα antagonist in utero; they were probably not known to be immunosuppressed at the time of vaccination. As a precaution, any infant who has been exposed to immunosuppressive treatment from

the mother either in utero during pregnancy or via breastfeeding should have any live attenuated vaccination deferred for as long as a postnatal influence on the immune status of the infant remains possible. In the case of in utero exposure to TNFα antagonists and other biological medicines, this period should be until the infant is age 6 months, after which time vaccination should be considered.

2) Shingles vaccination in elderly patients with immunosuppression
The MHRA has received Yellow Cards reporting that several elderly patients have received shingles vaccine (Zostavax) at a time when they were possibly immunosuppressed (eg, due to treatment for a transplant or due to lymphoproliferative disorders). The suspected adverse reactions reported in these Yellow Cards are possibly a consequence of a disseminated viral infection caused by the vaccine strain.

Reminder for healthcare professionals by the MHRA is as follows:

- Live attenuated vaccines should not routinely be given to people who are clinically immunosuppressed (either due to drug treatment or underlying illness).
- It is important for healthcare professionals who are administering a particular vaccine to be familiar with the contraindications and special precautions before proceeding with immunization.
- Specialists with responsibility for an immunosuppressed patient who may be in a group eligible for a live attenuated vaccine should include in their correspondence with primary care a statement of their opinion on the patient's suitability for the vaccine.
- If primary care professionals are in any doubt as to whether a person due to receive a live attenuated vaccine may be immunosuppressed at the time, immunisation should be deferred until secondary care specialist advice has been sought, including advice from an immunologist if required.
- Remember that close contacts of immunosuppressed individuals should be fully immunised to minimise the risk of infection of vaccine-preventable diseases in immunosuppressed individuals.

In Hong Kong, vaccines for human use are prescription only medicines. As on 13 June 2016, DH has received 21 cases of adverse event following immunization of live attenuated vaccines. In view of the above MHRA announcement, DH issued a letter to inform local healthcare professionals on 19 April 2016 to draw their attention on the above recommendation.

UK: Dimethyl fumarate (Tecfidera): updated advice on risk of progressive multifocal leukoencephalopathy

On 18 April 2016, MHRA announced that cases of progressive multifocal leukoencephalopathy (PML) have been reported in patients taking dimethyl fumarate for multiple sclerosis, who all had prolonged lymphopenia.

Dimethyl fumarate (Tecfidera) is authorised in UK to treat relapsing-remitting multiple sclerosis. This medicine can cause lymphopenia.

Dimethyl fumarate is associated with an increased risk of PML — a rare, progressive, and demyelinating disease of the central nervous system that can be fatal. It is caused by activation of the John Cunningham virus (JCV), which usually remains latent and typically only causes PML in immunocompromised patients.

In March 2015, the MHRA informed the public of a fatal case of PML in a patient participating in the open-label ENDORSE study of dimethyl fumarate in multiple sclerosis. In November 2015, the licence-holder sent a letter to health professionals regarding another 2 cases of PML in patients who had been taking dimethyl fumarate for multiple sclerosis. All three patients were male and had not received any other medicines known at the time to be associated with a risk of PML. All three were seropositive for anti-JCV antibodies at the time of PML diagnosis. A 4th confirmed case of PML has also been reported.

The MHRA advised healthcare professionals of the following:

1) Before starting dimethyl fumarate treatment

New advice:
- Perform a baseline cranial MRI scan as a reference, usually within 3 months of starting dimethyl fumarate treatment.

Reminder of previous advice:
- Perform a full blood count including lymphocyte subsets.
- Counsel patients and carers on the risk of PML; advise them on symptoms to watch out for and to get medical help urgently if they occur.
- If JCV testing is undertaken, consider that the influence of lymphopenia on the accuracy of the anti-JCV antibody test has not been studied in patients treated with dimethyl fumarate.

2) During dimethyl fumarate treatment

New advice:
- In any patient, if PML is suspected, stop dimethyl fumarate immediately and investigate appropriately, eg MRI scan; ultrasensitive polymerase chain reaction (PCR) assay for JCV DNA.
- Monitor full blood count every 3 months.
- Consider interrupting dimethyl fumarate if lymphocyte counts fall below $0.5x10^9$/L for more than 6 months.
- If treatment is stopped, monitor lymphocyte counts until they return to normal.
- Note that patients might still develop a JCV infection, even if they have a normal lymphocyte count and previously tested negative for anti-JCV antibodies.

Reminder of previous advice:
- Monitor patients for signs and symptoms or appearance of new neurological dysfunction (eg motor, cognitive, or psychiatric symptoms), bearing in mind that PML can present with features similar to multiple sclerosis.

3) If dimethyl fumarate treatment is continued in patients with severe prolonged lymphopenia

New advice:
- Consider further MRI imaging as part of increased vigilance for PML, in accordance with national and local recommendations.
- Counsel patients again on the risk of PML and remind them of the symptoms to watch out for.

In Hong Kong, there are two registered pharmaceutical products containing dimethyl fumarate, namely Tecfidera Gastro-resistant Capsules 120mg (HK-64411) and Tecfidera Gastro-resistant Capsules 240mg (HK-64410) which are registered by UCB Pharma (Hong Kong) Limited. Both products are prescription only medicines. Related news was previously issued by the US FDA, Health Canada, MHRA and EMA. As on 13 June 2016, DH has not received any ADR case related to dimethyl fumarate. The package insert of the local products has already included the warning on PML. In view of the above MHRA announcement, DH issued a letter to inform local healthcare professionals on 19 April 2016 to draw their attention on the new advice. DH will remain vigilant on the safety of medicines containing dimethyl fumarate.

UK: Natalizumab (Tysabri▼): progressive multifocal leukoencephalopathy - updated advice to support early detection

On 18 April 2016, MHRA advised that when treating patients with Natalizumab (Tysabri), perform a quantitative serum anti-JCV antibody test — including index value — to support risk stratification for PML. For high-risk patients, consider more frequent MRI screening.

Natalizumab (Tysabri) is a single disease-modifying therapy for adults with multiple sclerosis who have high disease activity despite treatment with beta-interferon, or who have rapidly evolving severe relapsing remitting disease.

Natalizumab is associated with a risk of PML — a rare, progressive, and demyelinating disease of the central nervous system that can be fatal. It is caused by activation of JCV, which usually remains latent and typically only causes PML in immunocompromised patients.

Up to August 2015, there had been 582 reports worldwide from clinical practice of PML in patients receiving natalizumab. Up to 30 March 2016, the MHRA had received 33 Yellow Card reports of PML in patients receiving natalizumab in UK. Evidence from these reports and several studies has led to new advice to reduce the risk of PML as listed below.

Clinically asymptomatic PML: importance of early detection

Recent analyses suggest that earlier detection of PML is associated with improved outcomes. Cases of asymptomatic PML, diagnosed based on MRI scans and positive JCV DNA in the cerebrospinal fluid, have been reported. PML which is clinically asymptomatic at diagnosis has more localised or unilobar lesions on MRI scans compared with symptomatic patients. Occasionally, particularly in patients with small lesions, exclusively grey matter involvement of PML has been observed on MRI scans.

Note that these analyses have important potential limitations, including lead time bias and length time bias. There was also information missing on MRI frequency in symptomatic PML cases, preventing comparison with PML cases asymptomatic at onset.

Therefore the risk-proportionate MRI screening protocol for PML described in this article is recommended for patients receiving natalizumab. It is also important that patients do not have any signs or symptoms of PML before switching to other disease-modifying treatments.

The risk of PML in patients receiving natalizumab is already known to be higher in patients who:

- are serum anti-JCV antibody positive;
- have had immunosuppressant therapy;
- have been receiving natalizumab for a long time (especially for more than 2 years).

Recent data show that in patients who have not had immunosuppressant therapy and are serum anti-JCV antibody positive, the risk of PML rises with increased serum anti-JCV antibody index.

Therefore, the following groups of patients have been defined as being at high risk of PML:

- those who have all three risk factors for PML (ie immunosuppressant therapy, serum anti-JCV antibody positive, and more than 2 years of natalizumab exposure);
- those who have not had immunosuppressant therapy but have a high serum anti-JCV antibody index and more than 2 years of natalizumab exposure.

For these high-risk groups, consider the extra precautions listed in the '2) During natalizumab treatment' section listed below.

The MHRA advised healthcare professionals of the following:

1) Before starting natalizumab treatment

New advice:

- Perform a baseline quantitative serum anti-JCV antibody test — including the index value — to support risk stratification for PML.

Reminder of previous advice:

- Perform a baseline cranial MRI scan as a reference, usually within 3 months of starting natalizumab treatment.
- Counsel patients and carers on the risk of PML — an updated Treatment Initiation Form in UK will be available in due course.
- Advise patients and carers on symptoms to watch out for and to get medical advice urgently if they occur.

2) During natalizumab treatment

New advice:

- Perform a quantitative serum anti-JCV antibody test — including the index value — every 6 months for the patients specified in the algorithm in the MHRA website (https://www.gov.uk/drug-safety-update/natalizumab-tysabri-progressive-multifocal-leukoencephalopathy-updated-advice-to-support-early-detection).
- For high-risk patients, consider the following extra precautions:
  - ◊ more frequent MRI screening for PML, such as every 3–6 months using an

abbreviated protocol (FLAIR, T2-weighted, and DW imaging): earlier detection of PML in asymptomatic patients may be associated with improved PML outcome.

◊ If PML is suspected, extend the MRI protocol to include contrast-enhanced T1 -weighted imaging and consider testing for JCV DNA in the cerebrospinal fluid using ultrasensitive PCR .

Reminder of previous advice (for all patients):

- If PML is suspected at any time, stop natalizumab treatment and investigate appropriately until PML has been excluded.
- Perform a quantitative serum anti-JCV antibody test — including the index value — for any patient with unknown antibody index (all patients should be tested at least once).
- Perform a full cranial MRI scan at least yearly for the entire duration of treatment, to have up-to-date reference images.
- Monitor patients for signs and symptoms or appearance of new neurological dysfunction (eg motor, cognitive, or psychiatric symptoms), bearing in mind that PML can present with features similar to multiple sclerosis.
- Consider PML in the differential diagnosis of any patient presenting with neurological symptoms or new brain lesions in their MRI scan – cases of asymptomatic PML, diagnosed based on MRI scans and positive JCV DNA in the cerebrospinal fluid, have been reported.
- After 2 years of treatment, remind patients of the risk of PML with natalizumab using the updated Treatment Continuation Form in UK, which will be available in due course.

3) After stopping natalizumab treatment:

New advice:

- Advise patients and carers to continue to watch out for signs and symptoms of PML for 6 months after the last dose — use the new Treatment Discontinuation Form in UK, which will be available in due course, to aid this discussion.
- Continue the same monitoring protocol for 6 months after the last dose, as PML has been reported during this time.

In Hong Kong, there is one registered pharmaceutical product containing natalizumab, namely Tysabri Concentrate for Solution for Infusion 300mg (HK-61519) which is registered by UCB Pharma (Hong Kong) Limited, and is a prescription only medicine. Related news was previously issued by EMA, and was reported in the Drug News Issue No. 72 and 76. DH issued a letter to inform local healthcare professionals on 15 February 2016 to draw their attention. The local package insert of the product has already included the warning on PML. As on 13 June 2016, DH has not received any ADR case related to natalizumab. In view of the above MHRA announcement, DH issued a letter to inform local healthcare professionals on 19 April 2016 to draw their attention on the new advice. As previously reported, the matter, including the above MHRA's updated advices, will be discussed by the Registration Committee.

UK: Fingolimod (Gilenya▼): risks of progressive multifocal leukoencephalopathy, basal-cell carcinoma, and opportunistic infections

On 18 April 2016, MHRA advised that the immunomodulatory effects of fingolimod increase the risk of PML and opportunistic infections.

Fingolimod (Gilenya) is authorised to treat relapsing-remitting multiple sclerosis in patients whose disease has failed to respond to beta-interferon or is severe and getting worse rapidly in UK.

A) Risk of PML

There have been reports of PML in patients taking fingolimod (none in UK). As of December 2015, 3 confirmed cases of PML had been reported in patients taking fingolimod who had not received natalizumab. In fingolimod patients previously treated with natalizumab, 17 suspected cases of PML had been reported. It is estimated that approximately 20,000 patients had received fingolimod after previous natalizumab treatment. PML is a rare, progressive, and demyelinating disease of the central nervous system that can be fatal. It is caused by activation of JCV,

which usually remains latent and typically only causes PML in immunocompromised patients.

New advice for healthcare professionals is as follows:

1) Before starting fingolimod treatment:
- Perform a full blood count including lymphocyte subsets.
- Perform a baseline cranial MRI scan as a reference, usually within 3 months of starting fingolimod treatment.
- Counsel patients and carers on the risk of PML; advise them on the symptoms to watch out for and to get medical help urgently if they occur.
- If testing for JCV is undertaken, consider that the influence of lymphopenia on the accuracy of the anti-JCV antibody test has not been studied in fingolimod-treated patients.

2) During fingolimod treatment
- If PML is suspected, stop fingolimod treatment immediately and investigate appropriately, eg MRI scan; ultrasensitive PCR assay for JCV DNA.
- Monitor full blood count 3 months after starting fingolimod treatment and at least yearly thereafter.
- Interrupt fingolimod treatment if lymphocyte count falls below $0.2x10^9$/L, do not restart treatment until lymphocyte levels have recovered.
- When analysing routine MRI scans, pay attention to PML-suggestive lesions.
- Consider further MRI scans as part of increased vigilance in patients considered at high risk of PML, in accordance with national and local recommendations.
- Monitor patients for signs and symptoms or appearance of new neurological dysfunction (eg motor, cognitive, or psychiatric symptoms), bearing in mind that PML can present with features similar to multiple sclerosis.
- Note that patients might still develop a JCV infection, even if they have a normal lymphocyte count and previously tested negative for anti-JCV antibodies.

Other multiple sclerosis treatments — natalizumab (Tysabri) and dimethyl fumarate (Tecfidera) — have also been linked to a risk of PML.

B) Risk of basal-cell carcinoma

Basal-cell carcinoma has been reported in patients taking fingolimod in clinical trials and in clinical practice. Up to 28 February 2015, 151 cases had been reported worldwide (exposure estimated at approximately 219,000 patient-years). Up to 30 March 2016, the MHRA had received 2 Yellow Card reports of basal-cell carcinoma in patients taking fingolimod.

New advice for healthcare professionals is as follows:
- Do not prescribe fingolimod to any patient with an active malignancy.
- Patients' skin should be evaluated before starting fingolimod treatment and then at least yearly during treatment.
- Inform patients about the common signs of basal-cell carcinoma and the need to seek medical advice if they occur. These include skin nodules (eg shiny pearly nodules), patches, or open sores that do not heal within weeks.
- Refer patients with any signs of basal-cell carcinoma to a dermatologist.

C) Risk of other opportunistic infections

The immunomodulatory effects of fingolimod can increase the risk of other central nervous system infections. These can be viral (eg herpes simplex, varicella zoster), fungal (eg cryptococcal meningitis), or bacterial (eg atypical mycobacterium). Up to 30 March 2016, the MHRA had received 49 Yellow Card reports of opportunistic infections in patients taking fingolimod.

Reminder of previous advice for healthcare professionals is as follows:
- Do not start fingolimod in any patient with severe infection.
- Monitor full blood count 3 months after starting fingolimod treatment, at least yearly thereafter, and in case of any signs of infection.
- Stop fingolimod treatment if a patient develops a serious infection; before

restarting fingolimod treatment:
  - ◊ ensure the infection has resolved.
  - ◊ carefully balance the benefit of fingolimod treatment against the risk of another infection.
- Fingolimod can take up to 2 months to be eliminated from the body after the last dose, so remain vigilant for infections during this period.

In Hong Kong, there is one registered pharmaceutical product containing fingolimod, namely Gilenya Hard Capsules 0.5mg (HK-61192) which is registered by Novartis Pharmaceuticals (HK) Ltd (Novartis), and is a prescription only medicine. Related news was previously issued by the US FDA, Health Canada and EMA, and was reported in the Drug News Issue No. 46, 70 and 71. DH issued letters to inform local healthcare professionals on 5 August 2015 and 2 October 2015 to draw their attention. As on 13 June 2016, DH has not received any ADR case related to fingolimod.

Novartis has applied to DH to update the package insert of the product to include the relevant warning of PML and basal cell carcinoma, and the application is under evaluation. In view of the above MHRA announcement, DH issued a letter to inform local healthcare professionals on 19 April 2016 to draw their attention on the new advice. As previously reported, the matter, including the above MHRA's updated advices, will be discussed by the Registration Committee.

UK: Aflibercept (Zaltrap▼): minimising the risk of osteonecrosis of the jaw

On 18 April 2016, MHRA advised that dental examination and appropriate preventive dentistry should be considered before treatment with Aflibercept (Zaltrap), especially for patients also treated with an intravenous bisphosphonate.

Zaltrap is authorised in UK in combination with irinotecan, 5-fluorouracil, and folinic acid (FOLFIRI) chemotherapy for treatment of adults with metastatic colorectal cancer that is resistant to, or has progressed after, treatment with an oxaliplatin-containing regimen. More than 22,000 patients worldwide are estimated to have received Zaltrap.

There have been 8 post-marketing cases of osteonecrosis of the jaw (ONJ) reported worldwide up to 3 August 2015, 3 of which stated concomitant treatment with intravenous bisphosphonates and 5 previous invasive dental procedure or infection (all of which are known risk factors for ONJ).

A meta-analysis of 3 phase III cancer clinical trials (EFC10262/VELOUR, EFC10261/VITAL, EFC10547/VANILLA) found that 3 of 1,333 patients assigned Zaltrap had ONJ, compared with 1 of 1,329 assigned placebo (relative risk for all-grade osteonecrosis 2.99 [95% CI 0.31–28.72]).

A further phase III cancer trial (EFC6546/ VENICE) identified a higher frequency of ONJ in patients treated with Zaltrap and docetaxel independent of bisphosphonate use (7 of 209 patients receiving Zaltrap, docetaxel, and bisphosphonates compared with 2 of 224 patients receiving placebo, doxetaxel, and bisphosphonates).

The mechanism by which Zaltrap may increase the risk of ONJ is not fully known. However, it is an antiangiogenic agent and might therefore interfere with, and decrease, new capillary growth during wound healing at sites of physical trauma such as after dental procedures. ONJ is a known risk with other antiangiogenic agents, such as sunitinib or bevacizumab, which target endothelial growth factor pathways.

Overall, although there are many known risk factors for ONJ, there is sufficient evidence to suggest that Zaltrap may independently increase or contribute to this risk.

Aflibercept is also the active ingredient in Eylea intravitreal injection, which is authorised for treatment of macular degeneration in UK. ONJ has not been identified as a risk for Eylea.

The MHRA advised healthcare professionals of the following:
- Patients who have also previously or concomitantly received an intravenous bisphosphonate may be at particular risk.

- Before starting treatment, consider whether a dental examination and any appropriate preventive dentistry are needed.
- Avoid invasive dental procedures, where possible, in patients being treated with Zaltrap who have previously received, or are currently receiving, an intravenous bisphosphonate.
- During treatment, advise patients to: maintain good oral hygiene; receive routine dental check -ups; and to report any oral symptoms such as dental mobility, pain, or swelling.

In Hong Kong, there are three registered pharmaceutical products containing aflibercept, namely Zaltrap Concentrate for Solution for Infusion 100mg/4ml (HK-62551) and Zaltrap Concentrate for Solution for Infusion 200mg/8ml (HK-62552) which are registered by Sanofi-aventis Hong Kong Limited, and Eylea Solution for Intravitreal Injection 40mg/ml (HK-61971) which is registered by Bayer Healthcare Ltd. All products are prescription only medicines. As on 13 June 2016, DH has received two ADR cases in connection with Zaltrap, but they were not related to ONJ. In view of the above MHRA announcement, DH issued a letter to inform local healthcare professionals on 19 April 2016 to draw their attention on the risk of ONJ with Zaltrap, and the matter will be discussed by the Registration Committee.

UK: Apomorphine with domperidone: minimising risk of cardiac side effects

On 18 April 2016, MHRA announced that patients receiving apomorphine and domperidone require an assessment of cardiac risk factors and ECG monitoring to reduce the risk of serious arrhythmia related to QT-prolongation.

Apomorphine (brand names: APO-go, Dacepton in UK) is a dopamine agonist used to treat refractory motor fluctuations in people with Parkinson's disease. Domperidone (brand names: Motilium, Dismotil in UK) is usually started at least two days before apomorphine to control the expected side effects of nausea and vomiting.

In 2014, a review by EU medicines regulators on risk of cardiac side effects of domperidone concluded that domperidone is associated with a small increased risk of QT-interval prolongation, serious ventricular arrhythmias, and sudden cardiac death. A higher risk was observed in people older than 60 years, people taking daily oral doses of more than 30 mg, and in those taking other QT-prolonging medicines or cytochrome P450 3A4 inhibitors at the same time as domperidone. As a result of this review, the licensed indication for domperidone was restricted to relief of nausea and vomiting, the licensed dose was reduced, and several contraindications were introduced in UK.

Apomorphine can increase the risk of QT-prolongation at high doses. A review by EU medicines regulators of the safety of concomitant apomorphine and domperidone use has recently finished. This review concluded that health professionals should take the precautions listed below to reduce the risk of QT-prolongation. The risk of QT-prolongation may be increased in people on concomitant apomorphine and domperidone who have certain risk factors, including:

- pre-existing QT-interval prolongation;
- serious underlying cardiac disorders such as heart failure;
- severe hepatic dysfunction;
- significant electrolyte disturbances;
- concomitant drug therapy that may increase domperidone levels (eg, cytochrome P450 3A4 inhibitors).

The MHRA advised healthcare professionals of the following:

- Before starting treatment, carefully consider whether the benefits of concomitant apomorphine and domperidone treatment outweigh the small increased risk of cardiac side effects.
- Discuss the benefits and risks of apomorphine with patients and carers and advise them to contact their doctor immediately if they develop palpitations or syncopal symptoms during treatment.
- Check the QT-interval before starting domperidone, during the apomorphine initiation phase and if clinically indicated thereafter (eg, if a QT-prolonging or interacting drug is started or if symptoms of cardiac side effects are reported).

Safety Update

- Regularly review domperidone treatment to ensure patients take the lowest effective dose for the shortest duration.
- Advise patients to inform their doctor of any changes that could increase their risk of arrhythmia, such as:
  - ◊ symptoms of cardiac or hepatic disorders;
  - ◊ conditions that could cause electrolyte disturbances (eg, gastroenteritis or starting a diuretic);
  - ◊ starting any other medicines.

In Hong Kong, there are three registered pharmaceutical products containing apomorphine, namely Apo-go Solution for Inj 10mg/ml (HK-58095), Apo-go PFS Solution for Infusion 5mg/ml (HK-58096) and Apo-go Pen Solution for Injection 10mg/ml (HK-61219), and 46 registered pharmaceutical products containing domperidone. All products are prescription only medicines. Related news on cardiovascular risk of domperidone was previously issued by various overseas drug regulatory authorities, and was reported in the Drug News Issue No. 29, 53, 59 and 63. DH issued a letter to inform local healthcare professionals on 8 March 2012 and 10 March 2014.

The matter was also discussed in the meeting of the Registration Committee on February 2012 and May 2014 with the following decision:

- To update the sales pack or package insert of domperidone-containing products to include the appropriate safety information related to cardiovascular risk.
- To deregister all suppositories containing domperidone with effect from 1 October 2014 as their benefits no longer outweigh the risks.
- To tighten control over oral domperidone products (previously as pharmacy medicines) so that they can only be sold by prescriptions at pharmacies under the supervision of pharmacists.

News on the risk with the concomitant use of domperidone and apomorphine has not been previously reported.

As on 13 June 2016, DH has not received any ADR case related to the concomitant use of domperidone and apomorphine.

In view of the above MHRA announcement, DH issued a letter to inform local healthcare professionals on 19 April 2016 to draw their attention on the risk, and the matter will be discussed by the Registration Committee.

Drug Recall

DH endorsed batch recall of Famotidine USP 20mg tablets (HK-54490)

On 15 April 2016, DH endorsed a licensed drug wholesaler, Eugenpharm International Ltd ("Eugenpharm"), to recall two batches (batch numbers: TE-4846 and TE-4847) of Famotidine USP 20mg tablets (HK-54490) from the market because the outer boxes of these products did not match with the registered particulars.

Acting on a complaint, investigation carried out at Eugenpharm found that outer boxes of a new design were used in the secondary packaging of these two batches of products. However, such change in the outer box had not been approved by the Pharmacy and Poisons Board and rendered the product unregistered. Since the supply of unregistered pharmaceutical products contravenes the Pharmacy and Poisons Regulations (Cap. 138A), Eugenpharm voluntary recalled the products from the market. DH's investigation was continuing.

The above product contains famotidine is an over-the-counter medicine used for the treatment of gastric ulcer and duodenal ulcer. According to Eugenpharm, about 10,000 boxes (each box contains 100 tablets) from the two affected batches have been supplied to private doctors and local pharmacies.

As on 13 June 2016, DH has not received any ADR case related to the products concerned. 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 Bandi Forte Enema 10ml (HK-61569)

On 26 April 2016, DH endorsed a licensed drug wholesaler, Hengan Pharmacare Co Ltd, to recall all batches of Bandi Forte Enema 10ml (Hong Kong registration number: HK-61569) from the market for a potential quality issue.

Upon notification from Hengan that the manufacturer in Taiwan was recalling the above product as it had been stored in an unauthorised facility in Taiwan, DH commenced follow-up investigations immediately.

The above product, containing glycerol and sodium chloride, is an over-the-counter medicine used for the treatment of constipation. According to Hengan, about 40 400 boxes (each containing 10 units) of the above product have been supplied to local pharmacies and medicine stores.

As on 13 June 2016, DH has not received any ADR case related to the above product. A notice was released on the website of the Drug Office on the same day to alert the public of the recall.

People who have used the above product should stop using it immediately and consult their healthcare professionals if feeling unwell or in doubt.

DH endorsed recall of Loradin tablets 10mg (HK-51131)

On 27 April 2016, DH endorsed a licensed drug wholesaler, Sincerity (Asia) Co. Ltd ("Sincerity"), to recall all batches of Loradin tablets 10mg (30-tablet and 100-tablet packs) (Hong Kong registration number: HK-51131) from the market because the outer boxes and package inserts of the product did not match with the registered particulars.

Acting on a public complaint, investigation carried out at Sincerity found that the outer boxes and package inserts of the product had been changed to new design. However, such changes were not approved by the Pharmacy and Poisons Board and rendered the product unregistered. Since the supply of unregistered pharmaceutical products contravenes the Pharmacy and Poisons Regulations (Cap. 138A), Sincerity voluntary recalled the product from the market. DH's investigation was continuing.

The above product, containing loratidine, is a medicine for the relief of allergic symptoms. According to Sincerity, about 3,000 boxes of the product have been imported and supplied to local pharmacies and medicine stores.

As on 13 June 2016, DH has not received any ADR case related to the product concerned. 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 nine products imported by Sincerity

On 29 April 2016, DH endorsed Sincerity to recall 9 products from the market because the outer boxes of these products did not match with the registered particulars. The 9 products are Cevinolon Cream 5% (HK-42511), Divon CR capsules 100mg (HK-52059), Partial tablets 15mg (HK-53675), Erdon-100 TR capsules 100mg (HK-55534), Herperax-400 tablets 400mg (HK-57680), Herperax-200 tablets 200mg (HK-57681), Erdon gel 1% (HK-50277), Ecozol-VT 150 vaginal tablets 150mg (HK-56293) and Omicap-20 capsules 20mg (HK-58610).

Further to the recall by Sincerity on 27 April 2016, DH investigation found out 9 more Sincerity's products packed with an outer box not approved by the Pharmacy and Poisons Board, rendered the products unregistered. Since the supply of unregistered pharmaceutical products contravenes the Pharmacy and Poisons Regulations (Cap.

Drug Recall

138A), Sincerity voluntary recalled the above 9 products from the market. DH's investigation was continuing.

According to Sincerity, the 9 products were mainly supplied to private doctors and local pharmacies. A notice was released on the website of the Drug Office on 29 April 2016 to alert the public of the recall

Drug Incident

DH urges public not to use product with undeclared medicines

On 25 April 2016, DH urged the public not to buy or use a product named as 大明黑骨藤长寿茶 as it was found to contain an undeclared Part 1 poison, diclofenac.

Upon notification by the Hospital Authority (HA) of a case affecting a male patient aged 63 who consumed the above product, DH commenced investigations immediately.

The patient was admitted to North District Hospital with confusion and acute renal injury. He described a history of consuming the above product, which was purchased locally. Preliminary laboratory test results by the HA revealed that the product might contain an undeclared Part 1 poison.

Subsequent to DH's follow-up investigations, a retail premises in Sheung Shui was raided on 23 April 2016 in an operation during which 49 bags of the above product were seized and sent to the Government Laboratory for analysis. Test results confirmed that the product contains diclofenac.

Oral products containing diclofenac are prescription medicines for the relief of pain and can only be supplied upon prescription at pharmacies under the supervision of a registered pharmacist. Side-effects of diclofenac include gastrointestinal discomfort, nausea and peptic ulcers.

News in Brief

Availability of a new registered BCG vaccine

On 6 April 2016, DH issued a letter to inform local healthcare professionals that a new BCG vaccine against tuberculosis has been registered in Hong Kong, namely BCG Vaccine, Freeze-dried Powder and Solvent for Suspension for Injection 0.5mg/ml, HK-registration number HK-64420. The above new BCG vaccine is a prescription only medicine.

Previously, there has been only one registered BCG vaccine against tuberculosis in Hong Kong, namely BCG Vaccine SSI Powder for Inj 0.75mg/ml (HK-44952), and is used in the Hong Kong Children Immunization Programme. DH is aware that there has been a shortage of supply of the vaccine in many overseas places and including Hong Kong since 2015, and it is foreseen that the shortage situation will likely continue in 2016.

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.