Drug News
藥 物 情 報

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This is a monthly digest of local and overseas drug safety news released by the Drug Office of the Department of Health in November 2020 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: Concomitant use of Opsumit® (macitentan) Film-Coated Tablet 10mg with dual moderate CYP3A4 ／ CYP2C9 inhibitors that could result in an increase in exposure to Opsumit®

On 9 November 2020, the Health Sciences Authority (HSA) of Singapore announced that a Dear Healthcare Professional Letter has been issued by Johnson & Johnson Pte Ltd to inform healthcare professionals of a potential drug-drug interaction between Opsumit® (macitentan) and dual moderate CYP3A4/CYP2C9 inhibitors that could result in an increase in systemic exposure to Opsumit®.

A review has found CYP2C9 to be responsible for 26% of metabolism of macitentan as opposed to the previous understanding that it would provide a minor contribution. Co-administration of fluconazole (400 mg qd), a dual moderate CYP2C9 and CYP3A4 inhibitor, could result in a 3.8-fold increase in macitentan exposure due to the dual inhibition of the two most important metabolic pathways. Nonetheless, no safety concerns have been identified with the concurrent administration of dual CYP3A4/CYP2C9 inhibitors (e.g. fluconazole/amiodarone) and macitentan 10 mg and there is no change in the current recommended dose of macitentan 10 mg once daily. The package insert for Opsumit® in Singapore will be updated accordingly to reflect the new drug-drug interaction information. Healthcare professionals are advised to exercise caution when macitentan is administered concomitantly with moderate dual inhibitors of CYP3A4 and CYP2C9, or with both a moderate CYP3A4 inhibitor and a moderate CYP2C9 inhibitor.

In Hong Kong, Opsumit Tablets 10mg (HK-64419) is a registered pharmaceutical product containing macitentan. The product is registered by Johnson & Johnson (Hong Kong) Ltd., and is a prescription-only medicine. As on 7 December 2020, the Department of Health (DH) has received 10 cases of adverse drug reaction (ADR) related to macitentan, but these cases are not related to drug interaction. In light of the above HSA's announcement, the DH issued a letter to inform local healthcare professionals to draw their attention on 11 November 2020. The DH will remain vigilant on safety update of the drug issued by other overseas drug regulatory authorities.

UK: Isotretinoin: an expert review of suspected psychiatric and sexual side effects

On 10 November 2020, the Medicines and Healthcare products Regulatory Agency (MHRA) of the United Kingdom (UK) announced that it is currently reviewing the safety of isotretinoin.

Isotretinoin can cause side effects in some people, and in some cases these can be severe. Details about the possible side effects including psychiatric (mental health) and sexual effects are provided in the leaflet with the medicine in the UK. The safety of isotretinoin has been closely monitored throughout its lifecycle, with information for prescribers and patients being updated as significant new data has become available. There are ongoing patient concerns about the safety of isotretinoin. In particular, whether in some cases, the suspected psychiatric and sexual side effects continue after isotretinoin has been stopped. The Commission on Human Medicines has established an independent review of the available evidence by the Isotretinoin Expert Working Group (IEWG). Following completion of the review, a report of the IEWG's conclusions and recommendations will be published. It is anticipated that the final report will be published in 2021.

The MHRA is inviting interested individuals including patients, patient representatives, healthcare professionals, researchers, and organisations to provide their views.

In Hong Kong, there are 11 registered pharmaceutical products containing isotretinoin. All products are prescription-only medicines. As on 7 December 2020, the DH has received 2 cases of ADR related to isotretinoin, but these cases are not related to psychiatric and sexual side effects.

Related news was previously issued by the MHRA, and was reported in the Drug News Issue No. 96. The DH issued a letter to inform local healthcare professionals to draw their attention on 27 October 2017.

Currently, it is a requirement that package insert of local isotretinoin-containing products should include warnings about suicide and suicidal attempts. The package insert should also include safety information on sexual dysfunction including erectile dysfunction and decreased libido.

The DH will remain vigilant on safety update of the drug issued by the MHRA and other overseas drug regulatory authorities.

Singapore: Tecentriq® (atezolizumab): A new identified risk of severe cutaneous adverse reactions

On 11 November 2020, the HSA announced that a Dear Healthcare Professional Letter has been issued by Hoffman-La Roche to update healthcare professionals on a new identified risk of severe cutaneous adverse reactions (SCARs) associated with the use of Tecentriq®. Based on the totality of evidence in a recent analysis, SCARs are now considered to be an identified risk for atezolizumab. Consequently, the Tecentriq® package insert in Singapore will be updated to reflect the safety information on this risk. Healthcare professionals are advised to refer suspected cases of SCARs to a dermatologist for further diagnosis and management, to withhold atezolizumab from patients with suspected Stevens Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN) and to permanently withdraw atezolizumab for any grade confirmed SJS or TEN. Caution is advised when considering the use of atezolizumab in a patient who has previously experienced a severe or life-threatening skin adverse reaction on prior treatment with other immune-stimulatory anticancer agents.

In Hong Kong, Tecentriq Concentrate for Solution for Infusion 1200mg/20ml (HK-65567), Tecentriq Concentrate for Solution for Infusion 1200mg/20ml (HK-66341) and Tecentriq Concentrate for Solution for Infusion 840mg/14ml (HK-66613) are pharmaceutical products containing atezolizumab. All products are registered by Roche Hong Kong Limited, and are prescription-only medicines. As on 7 December 2020, the DH has received 74 cases of ADR related to atezolizumab, but these cases are not related to Stevens Johnson syndrome and toxic epidermal necrolysis. In light of the above HSA's announcement, the DH issued a letter to inform local healthcare professionals to draw their attention on 13 November 2020. The DH will remain vigilant on safety update of the drug issued by other overseas drug regulatory authorities.

EU: Ulipristal acetate for uterine fibroids: EMA recommends restricting use

On 13 November 2020, the European Medicines Agency (EMA) of the European Union (EU) announced that the EMA's human medicines committee, the Committee for Medicinal Products for Human Use (CHMP), has recommended restricting use of medicines containing ulipristal acetate 5 mg (Esmya and generic medicines) as a result of cases of serious liver injury. The medicines can now only be used to treat uterine fibroids in premenopausal women for whom surgical procedures (including uterine fibroid embolisation) are not appropriate or have not worked. The medicines must not be used for controlling symptoms of uterine fibroids while awaiting surgical treatment.

Information on the risk of liver failure (requiring liver transplantation in some cases) will be added to the summary of product characteristics and the package leaflets for ulipristal acetate 5 mg medicines as well as in educational material for doctors and cards for patients in the EU.

The EMA's safety committee, the Pharmacovigilance Risk Assessment Committee (PRAC), review of serious liver injury with ulipristal acetate 5 mg had found that it was not possible to identify either patients most at risk of liver injury or measures that could reduce the risk. The PRAC had therefore advised that these medicines should not be marketed in the EU.

The CHMP endorsed the PRAC's assessment of the risk of liver injury. However, it considered that the benefits of ulipristal acetate 5 mg in controlling fibroids may outweigh this risk in women who have no other treatment options. As a result, the CHMP recommended that the medicine remains available to treat premenopausal women who could not have surgery (or for whom surgery had not worked).

Ulipristal acetate is also authorised as a single-dose medicine for emergency contraception (ellaOne and other trade names). No concern has been raised about liver injury with these single-dose emergency contraception medicines and this recommendation does not affect them.

The CHMP recommendation will be forwarded to the European Commission for its decision. The use of 5-mg ulipristal acetate medicines for uterine fibroids had been suspended as a precaution while awaiting the outcome of this review.

Information for patients

- Their doctor will prescribe ulipristal acetate 5 mg medicine for treating uterine fibroids (growths in the womb that are not cancerous) only if:
  - they have not reached the menopause and
  - they cannot have an operation for the condition or the operation has not worked.
- Serious liver injury has occurred in women taking ulipristal acetate 5 mg, which can lead to liver transplantation in a few cases. Their doctor will discuss with them whether their need for treatment outweighs this risk.
- They will have a blood test to check their liver before they take ulipristal acetate 5 mg, during their treatment and after their treatment stops.
- Read the card they have been given with their ulipristal acetate 5 mg medicine because it tells them what to do if they have any signs of liver injury.
- They must stop treatment with ulipristal acetate 5 mg and speak with their doctor immediately if they get any signs of liver injury such as yellowing of the skin, dark urine, feeling sick or vomiting.
- Speak to their doctor or pharmacist if they have any questions and concerns about their treatment.

Information for healthcare professionals

- Ulipristal acetate 5 mg medicine must only be prescribed for treating uterine fibroids in premenopausal women who cannot have surgery or uterine fibroid embolisation, or the surgical procedure has failed.
- Use of ulipristal acetate 5 mg is restricted because of reports of serious liver injury, occasionally requiring liver transplantation.
- Before treatment with ulipristal acetate 5 mg:
  - prescribers should discuss all available treatment options with women
  - prescribers should counsel women on the risk of liver failure and subsequent need for liver transplantation.
- Although risk factors for liver injury with ulipristal acetate 5 mg or specific measures to reduce risk have not been identified, healthcare professionals should follow the summary of product characteristics (including contraindications and recommendations on liver function monitoring) as well as the physician's guide to prescribing that is available for the medicine.
- Patients should be advised to monitor for signs and symptoms of liver damage.

Ulipristal acetate 5 mg was authorised for treating moderate to severe symptoms of uterine fibroids (non-cancerous tumours of the womb) in women who had not reached the menopause. It was used either for up to 3 months before surgery to remove the fibroids or over the long-term but with treatment breaks in women who could not have surgery.

In Hong Kong, Esmya (ulipristal acetate) Tablets 5mg (HK-62553) is a pharmaceutical product registered by Orient Europharma Co. Ltd, and is a prescription-only medicine. As on 7 December 2020, the DH has not received any case of ADR related to Esmya.

Related news on the previous review of Esmya was previously issued by various overseas drug regulatory authorities, and was reported in the Drug News Issue No. 98, 100, 103, 106 and 114. The DH issued a letter to inform local healthcare professionals to draw their attention on the risk of serious liver injury on 12 February 2018. In December 2018, the Registration Committee of the Pharmacy and Poisons Board (Registration Committee) discussed the matter, and decided that the sales pack or package insert of the product should include the relevant safety information.

Related news on the recent review of Esmya was previously issued by various overseas drug regulatory authorities, and was reported in the Drug

News Issue No. 125, 131 and 132. The DH issued a letter to inform local healthcare professionals to draw their attention on the EMA's recommendation to suspend ulipristal acetate for uterine fibroids on 16 March 2020.

On 20 March 2020, the DH endorsed Orient Europharma Co. Ltd to voluntarily recall Esmya Tablets 5mg (HK-62553) from patients due to the potential risk of liver injury. The recall was reported in the Drug News Issue No. 125 and was completed.

As previously reported, the matter will be discussed by the Registration Committee.

EU: Nitrosamines: EMA aligns recommendations for sartans with those for other medicines

On 13 November 2020, the EMA announced that the CHMP has aligned recommendations for limiting nitrosamine impurities in sartan medicines with recent recommendations it issued for other classes of medicines.

The main change concerns the limits for nitrosamines, which previously applied to the active ingredients but will now apply instead to the finished products (e.g. tablets). These limits, based on internationally agreed standards (The International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) M7(R1)), should ensure that the excess risk of cancer from nitrosamines in any sartan medicines is below 1 in 100,000 for a person taking the medicine for lifelong treatment.

In line with previous recommendations, companies should have appropriate control strategies to prevent or limit the presence of nitrosamine impurities as much as possible and, where necessary, improve their manufacturing processes. Companies should also evaluate the risk of nitrosamines being present in their medicines and carry out appropriate tests.

Nitrosamines are classified as probable human carcinogens (substances that could cause cancer). In the vast majority of sartan medicines, these impurities were either not found or were present at very low levels.

The CHMP concluded its review of sartan medicines in January 2019. The committee subsequently conducted a wider review, taking into account the experience from sartans and other medicines where nitrosamines were detected. The revised conditions companies need to fulfil for sartans brings them in line with those for other classes of medicines issued in June 2020.

The review of sartans concerned candesartan, irbesartan, losartan, olmesartan and valsartan, which belong to a class of medicines called sartans (also known as angiotensin-II-receptor antagonists).

These sartan medicines have a specific ring structure (tetrazole) whose synthesis could potentially lead to the formation of nitrosamine impurities. Other sartan medicines which do not have this ring, such as azilsartan, eprosartan and telmisartan, were not included in this review but are covered by the subsequent review of other medicines.

Sartans are used to treat patients with hypertension (high blood pressure) and those with certain heart or kidney diseases. They work by blocking the action of angiotensin II, a hormone that constricts blood vessels and causes blood pressure to rise.

In Hong Kong, as on 7 December 2020, there are 256 registered pharmaceutical products containing valsartan (94 products), candesartan (21 products), irbesartan (61 products), losartan (61 products) and olmesartan (19 products). All products are prescription-only medicines.

Regarding impurities in sartan-containing products, a public announcement was first issued on 6 July 2018, and the DH issued letters to inform local healthcare professionals on 6 July 2018, 9 July 2018, 25 July 2018 and 3 August 2018. Related news was also previously issued by various overseas drug regulatory authorities, and was reported in the Drug News Issue No. 105, 106, 107, 108, 109, 110, 111, 112, 113 and 114.

Regarding the announcements issued by various overseas drug regulatory authorities on the detection of *N*-nitrosodimethylamine (NDMA) and *N*-nitrosodiethylamine (NDEA) in sartan-containing products, the following 5 valsartan products and 1 irbesartan product were affected and recalled from the Hong Kong market on 6 July 2018 and 20 December 2018 respectively: HK-61786, HK-61787, HK-61784,

HK-61785, HK-60794 and HK-63378. The recalls were reported in the Drug News Issue No. 105 and 110. The DH noted that these recalls were completed.

The DH had collected samples of sartan-containing products in the local market for analysis. No NDMA and NDEA were detected.

Regarding the announcements issued by various overseas drug regulatory authorities on the detection of *N*-nitroso-*N*-methyl-4-aminobutyric acid (NMBA) in losartan, the DH endorsed the recall of 4 losartan products (HK-61932, HK-61933, HK-62634 and HK-62635) from the local market as a precautionary measure due to the potential for NMBA in the products on 11 March 2019. The recall was reported in the Drug News Issue No. 113. The DH noted that the recall was completed.

As on 7 December 2020, the DH has received 33 cases of ADR related to valsartan, candesartan, irbesartan, losartan and olmesartan. None of them is concluded to be related to the presence of impurities such as NDMA, NDEA and/or NMBA. The DH has provided update information at Drug Office's website (www.drugoffice.gov.hk) and will keep vigilant on any safety updates on detection of impurities in sartan-containing products issued by overseas regulatory authorities.

Patients who are taking sartan-containing products should not stop taking the medicines, but should seek advice from their healthcare professionals as soon as possible for proper arrangement.

UK: Pirfenidone (Esbriet): risk of serious liver injury; updated advice on liver function testing

On 16 November 2020, the MHRA announced that serious liver injury has been reported during treatment with pirfenidone in the first year after initiation, including 2 cases with a fatal outcome.

Pirfenidone is known to commonly cause elevation of liver transaminases (alanine aminotransferase (ALT) and aspartate aminotransferase (AST)), with associated concomitant increases in bilirubin in rare cases. A recent European review of safety data identified severe cases of drug-induced liver injury associated with pirfenidone reported post-marketing, including isolated cases with a fatal outcome. Reported events included hepatitis, liver injury, and liver failure. Reports of serious liver injury are considered to be uncommon (may occur in between 1 in 100 and 1 in 1000 people who take pirfenidone) and the benefit-risk profile of pirfenidone in the approved indications remains favourable. Although the aetiology is unclear, idiosyncratic reactions may underlie the occurrence of drug-induced liver injury following treatment with pirfenidone.

Two fatal cases consistent with drug-induced liver injury were reported in the literature in association with pirfenidone. These events of drug-induced liver injury and subsequent liver failure occurred at 1 month and 12 months after initiation of treatment with pirfenidone.

Following the findings of the review, existing warnings for the potential for hepatotoxicity in the product information will be strengthened to include the risk of clinically relevant drug-induced liver injury with pirfenidone. While the recommendation for liver function monitoring before and during treatment has not changed, new advice will be added to minimise risk in patients taking pirfenidone. New warnings in the summary of product characteristics in the UK will ask for prompt liver function testing in patients who report symptoms or have clinical signs that might indicate liver injury, and adjustment of the dose of pirfenidone or discontinuation of treatment if necessary.

It is recommended to perform liver function tests (ALT, AST, and bilirubin) before initiating treatment with pirfenidone, and subsequently at monthly intervals for the first 6 months, and then every 3 months thereafter. Clinically evaluate and perform liver function tests in patients who report symptoms that may indicate liver injury, including fatigue, anorexia, right upper abdominal discomfort, dark urine, or jaundice. In the event of significant elevation of liver aminotransferases or clinical signs and symptoms of hepatic injury, adjust the dose or discontinue treatment according to the new guidance.

Advice for healthcare professionals:

- Serious cases of drug-induced liver injury, including liver failure, have been reported in patients treated with pirfenidone; cases have been estimated to be of uncommon frequency but 2 reports worldwide had a fatal outcome.
- Continue to monitor ALT, AST, and bilirubin levels before initiation, at monthly intervals during the first 6 months of treatment and

every 3 months thereafter.
- Advise patients to seek medical help immediately if they have signs and symptoms that may indicate liver injury, including fatigue, anorexia, right upper abdominal discomfort, dark urine, or jaundice.
- Perform prompt clinical evaluation and measure liver function in patients who report symptoms that may indicate liver injury.
- In the event of significant elevation of liver enzymes or clinical signs and symptoms of liver injury, adjust the dose of pirfenidone or discontinue treatment.
- Monitor closely for signs of toxicity if pirfenidone is being used concomitantly with inhibitors of one or more other CYP isoenzymes involved in the metabolism of pirfenidone.

In Hong Kong, Esbriet Capsules 267mg (HK-64288) is a registered pharmaceutical product containing pirfenidone. The product is registered by Roche Hong Kong Limited, and is a prescription-only medicine. As on 7 December 2020, the DH has received one case of ADR related to pirfenidone, but this case is not related to liver injury. Related news was previously issued by the HSA and Health Canada, and was reported in the Drug News Issue No. 122 and 131. The DH issued a letter to inform local healthcare professionals to draw their attention on 19 December 2019. As previously reported, the matter will be discussed by the Registration Committee.

UK: Ferric carboxymaltose (Ferinject▼): risk of symptomatic hypophosphataemia leading to osteomalacia and fractures

On 16 November 2020, the MHRA announced the risk of symptomatic hypophosphataemia leading to osteomalacia and fractures associated with the use of ferric carboxymaltose.

Ferinject has been associated with common cases of hypophosphatemia (low blood phosphate). A recent European review concluded that ferric carboxymaltose is associated with hypophosphataemic osteomalacia (inadequate mineralisation of the bone matrix leading to softening of the bones). The review recommended strengthened advice to make healthcare professionals aware that osteomalacia can be a consequence of hypophosphataemia and to ensure early detection and effective management of hypophosphataemic osteomalacia. Based on the available data, it is difficult to estimate the magnitude of the risk of hypophosphataemic osteomalacia with ferric carboxymaltose, therefore the risk of this adverse reaction is included in the product information with a frequency category of not known.

As of 14 February 2020, the review considered 36 spontaneous cases worldwide in patients with concurrent hypophosphataemia associated with ferric carboxymaltose. Osteomalacia was reported in 28 cases and hypophosphataemic osteomalacia in 6 cases, with 2 cases reporting both terms. As of February 2020, the worldwide estimated exposure to ferric carboxymaltose was estimated to be 12,491,000 patient-years (168,632,771 defined daily doses). In most cases (30 [83%]) hypophosphataemia was reported as medically significant (moderate to severe) using a phosphate cut-off of lower than 2.0 milligram per decilitre. Where reported the patient age was 26–39 years in 8 cases, 40–56 years in 12 cases, 57–68 years in 4 cases, and 73–81 years in 3 cases. Where dosing information was reported, 13 patients had been given doses of 1000mg per infusion of ferric carboxymaltose for an average of 19 infusions over a period of 5–24 months. The time to onset of osteomalacia after starting treatment with ferric carboxymaltose at 1000mg dose was reported in 6 cases and ranged from 3 months to 5 years (median 14.5 months).

Of the 36 cases, 24 cases reported one or more reliable diagnostic criteria for osteomalacia: alkaline phosphatase (12 cases), parathyroid hormone (12 cases), magnetic resonance imagery (11 cases), bone scan (5 cases), bone biopsy (3 cases), and bone densitometry (2 cases). All 36 cases presented with one or more risk factors for osteomalacia, namely inflammatory bowel disease (14 cases), vitamin D deficiency (9 cases), osteoporosis (8 cases), malabsorption (6 cases), Rendu-Osler disease (6 cases), hyperparathyroidism (6 cases), long-term steroid use (6 cases), and chronic use of antacid therapies (3 cases).

Approximately half of the patients (19 of 36; 53%) developed one or more fractures (where reported, femoral neck fracture or pelvic or hip fracture) in conjunction with osteomalacia. Where reported, the outcome for the patient was recovered in 7 cases and recovering in 9 cases. The patients were treated with phosphate, calcium and/or vitamin D supplements. Where required, surgical treatment

was provided for fractures.

In the UK up to 22 October 2020, the MHRA has received 28 Yellow Card reports of hypophosphataemia and 2 reporting cases of hypophosphataemic osteomalacia with Ferinject. These cases in the UK were considered as part of the European review.

Hypophosphataemia (of uncommon frequency) is a listed adverse effect in association with Monofer▼ (iron isomaltoside, now known as ferric derisomaltose). Up to 1 January 2020, although cases have been reported of hypophosphatemia (including some serious cases), the MHRA is not aware of any cases reported of hypophosphataemic osteomalacia in association with ferric derisomaltose worldwide. As of February 2020, ferric derisomaltose has a worldwide exposure of 3,216,000 patient-years (based on a defined daily dose of 100mg iron equivalent). Up to 22 October 2020, the Yellow Card scheme has received 2 reports of hypophosphataemia with Monofer and the MHRA is not aware of any cases of osteomalacia.

The risk of persistent hypophosphatemia and osteomalacia may be higher with ferric carboxymaltose than with other intravenous iron formulations. A key mechanism postulated is that the carbohydrate moieties in ferric carboxymaltose may disproportionately inhibit degradation of fibroblast growth factor 23 (FGF23), which can result in increased FGF23 activity and ultimately greater renal phosphate wasting.

Advice for healthcare professionals:

- Ferric carboxymaltose is known to be commonly associated with hypophosphatemia.
- Cases have been reported of symptomatic hypophosphataemia leading to infrequent reports of hypophosphataemic osteomalacia and fractures in patients with existing risk factors and following prolonged exposure to high doses, some cases required clinical intervention, including surgery.
- Monitor serum phosphate levels in patients:
  - requiring multiple administrations of ferric carboxymaltose at higher doses
  - on long-term treatment with ferric carboxymaltose
  - with pre-existing risk factors for hypophosphataemia such as vitamin D deficiency, calcium and phosphate malabsorption, secondary hyperparathyroidism, inflammatory bowel disease, and osteoporosis.
- Advise patients to seek medical advice if they experience symptoms indicative of hypophosphataemia, including new musculoskeletal symptoms or worsening of tiredness, be aware these symptoms may be confused with those of iron deficiency anaemia.
- If hypophosphataemia persists, re-evaluate treatment with ferric carboxymaltose.

In Hong Kong, Ferinject Solution for Injection/ Infusion 100mg/2ml (HK-64137) and Ferinject Solution for Injection/Infusion 500mg/10ml (HK-64138) are pharmaceutical products containing ferric carboxymaltose. These products are registered by Zuellig Pharma Ltd, and are prescription-only medicines. As on 7 December 2020, the DH has not received any case of ADR related to ferric carboxymaltose.

Related news on the risk of hypophosphataemia associated with the use of ferric carboxymaltose was previously issued by Australia Therapeutic Goods Administration (TGA), and was reported in the Drug News Issue No. 124. The DH issued a letter to inform local healthcare professionals to draw their attention on 28 February 2020. The matter has been discussed by the Registration Committee on 7 December 2020 and decided that the sales pack labels and/or package inserts of registered pharmaceutical products containing ferric carboxymaltose (Ferinject) should include warning about the risk of hypophosphataemia and hypophosphataemic osteomalacia.

UK: Bupropion (Zyban): risk of serotonin syndrome with use with other serotonergic drugs

On 16 November 2020, the MHRA announced that cases of serotonin syndrome have been identified in associated with bupropion, especially in overdose or when bupropion is administered with other drugs with a serotonergic effect.

A recent European review of safety data for Zyban identified at least 8 cases of serotonin syndrome, a potentially life-threatening condition, where a possible interaction between bupropion and a serotonergic drug was thought to have led to serotonin syndrome. The review also identified 6 cases with good evidence of an association with an overdose of bupropion. In the majority of these

cases the patients had intentionally taken more than the prescribed dose.

The product information in the UK has been updated to include post-marketing reports of serotonin syndrome when bupropion is co-administered with a serotonergic agent such as selective serotonin reuptake inhibitors (SSRIs) or serotonin norepinephrine re-uptake inhibitors (SNRIs). If concomitant treatment with other serotonergic agents is clinically warranted, the patient should be advised of the milder symptoms of serotonin syndrome and told to seek advice should they occur, particularly during treatment initiation and dose increases. Advice that serotonin syndrome has been reported in cases of overdose also been included in the product information in the UK.

In the UK up to October 2020, the Yellow Card scheme has received 3 reports of serotonin syndrome associated with bupropion, one of which was a potential overdose of bupropion and two of which were associated with concomitant use of antidepressant medicines.

Serotonin syndrome is an iatrogenic disorder of serotonergic hyperstimulation in which the underlying mechanism is thought to involve excessive stimulation of 5-HT1A receptors. It occurs most commonly when two or more serotonergic agents with different pharmacological mechanisms are administered either concurrently or sequentially without a sufficient washout period. However, it can also be associated with a single serotonergic agent, particularly at a high dose. Signs and symptoms of serotonin syndrome may include mental-status changes (e.g. agitation, hallucinations, coma), autonomic instability (e.g. tachycardia, labile blood pressure, hyperthermia), neuromuscular abnormalities (e.g. hyperreflexia, incoordination, rigidity), and gastrointestinal symptoms (e.g. vomiting, diarrhoea).

If serotonin syndrome is suspected, a dose reduction or discontinuation of bupropion therapy should be considered, depending on the severity of the symptoms.

Advice for healthcare professionals:

- Cases of serotonin syndrome have been reported in association with bupropion and coadministration with serotonergic drugs, e.g. SSRIs, SNRIs.
- If concomitant prescribing with other serotonergic drugs is clinically warranted:
  - ➢ do not exceed the recommended dose
  - ➢ remind patients of the milder symptoms of serotonin syndrome at initiation of treatment and at any change of dose and the importance of seeking medical advice if they occur.
- If serotonin syndrome is suspected, either decrease the dose of bupropion or withdraw therapy depending on the severity of the symptoms.

In Hong Kong, there are 5 registered pharmaceutical products containing bupropion, and all products are prescription-only medicines. As on 7 December 2020, the DH has received 4 cases of ADR related to bupropion. In light of the above MHRA's announcement, the DH issued a letter to inform local healthcare professionals to draw their attention on 17 November 2020, and the matter will be discussed by the Registration Committee.

EU: Update to information on psychiatric disorders for chloroquine and hydroxychloroquine

On 27 November 2020, the EMA announced that the PRAC has recommended updating the product information for all chloroquine or hydroxychloroquine-containing medicines following a review of all available data that confirmed a link between the use of these medicines and the risk of psychiatric disorders and suicidal behaviour.

The review was initiated in May 2020 after the EMA had been informed by the Spanish Medicines Agency, Agencia Española de Medicamentos y Productos Sanitarios (AEMPS), of six cases of psychiatric disorders in patients with Coronavirus Disease 2019 (COVID-19) who were given higher than authorised doses of hydroxychloroquine. Chloroquine and hydroxychloroquine are authorised in the EU for the treatment of certain autoimmune diseases, such as rheumatoid arthritis and lupus, as well as for prophylaxis and treatment of malaria. They are not authorised for the treatment of COVID-19, but both medicines have been used as off-label treatment in patients with the disease. However, chloroquine and hydroxychloroquine have not shown any beneficial effects in treating COVID-19 in large randomised clinical trials.

In view of their use during the COVID-19

Safety Update

pandemic, the EMA had reminded healthcare professionals of the risks of these medicines in April and in May 2020. It is already known that chloroquine and hydroxychloroquine, even used in approved doses for authorised indications, can cause a wide spectrum of psychiatric disorders. Psychotic disorders and suicidal behaviour are listed in the product information of some chloroquine or hydroxychloroquine-containing medicines as rare side effects or side effects occurring at an unknown frequency.

The review confirmed that psychiatric disorders have occurred and may sometimes be serious, both in patients with and without prior mental health problems. Based on the available data, the review showed that, for hydroxychloroquine, the side effects may occur in the first month after the start of treatment. For chloroquine, there was not sufficient data to establish a clear timeframe.

The PRAC recommends updating the product information for these medicines to provide better information to healthcare professionals and patients on the risk of suicidal behaviour and psychiatric disorders.

Patients using chloroquine or hydroxychloroquine medicines who experience mental health problems (e.g. irrational thoughts, anxiety, hallucinations, feeling confused or feeling depressed, including thoughts of self-harm or suicide), or others around them who notice these side effects, should contact a doctor straight away.

In Hong Kong, there are 5 registered pharmaceutical products containing hydroxychloroquine, and all products are prescription-only medicines. There is no registered pharmaceutical product containing chloroquine. As on 7 December 2020, the DH has received 4 cases of ADR related to hydroxychloroquine, but these cases are not related to suicidal behaviour or psychiatric disorders. The DH has not received any case of ADR related to chloroquine.

Rare adverse effects of chloroquine and hydroxychloroquine about mental changes including psychotic episodes and hallucinations, delirium, anxiety, and agitation, insomnia, depression, and personality changes are documented in overseas reputable drug references such as the "Martindale: The Complete Drug Reference". In light of the above EMA's announcement, the DH issued a letter to inform local healthcare professionals to draw their attention on 30 November 2020, and the matter will be discussed by the Registration Committee.

Drug Recall

DH endorsed recall of Salonpas Advanced Formula Patches two-patches pack (HK-50034)

On 11 November 2020, the DH endorsed a licensed drug wholesaler, Hisamitsu Pharmaceutical (Hong Kong) Co., Limited (Hisamitsu), to recall all batches of the two-patches pack of Salonpas Advanced Formula Patches (HK-50034) from the market as a precautionary measure due to a quality issue.

The DH received notification from Hisamitsu that all batches of the two-patches pack of Salonpas Advanced Formula Patches are being recalled in Japan, as the content of one of the active ingredients in the product concerned failed to meet the product specifications during a long-term stability study. Although the product would not cause health harm to users, the quality issue might affect product efficacy. As a precautionary measure, Hisamitsu is recalling the relevant pack size of the product in Hong Kong.

Salonpas Advanced Formula Patches, containing methyl salicylate, menthol, camphor and vitamin E, is an over-the-counter medicine used externally for the treatment of muscle pain. The product was distributed by DKSH Hong Kong Ltd. According to the distributor, two-patches packs have been supplied to pharmacies, medicine stores and some local trading companies free of charge as samples. Some products were also re-exported to Macao.

Patients who are using the above product should seek advice from their healthcare professionals for appropriate arrangements.

As on 7 December 2020, the DH has not received any adverse reaction reports in connection with the product. Press release was posted on the Drug Office website on 11 November 2020 to alert the public of the product recall.

DH endorsed batch recall of Extraneal Peritoneal Dialysis Solution with 7.5%

Drug Recall

Icodextrin (HK-46627)

On 20 November 2020, the DH endorsed a licensed medicine wholesaler, Baxter Healthcare Ltd. (Baxter), to recall a batch (lot number: S20A31028) of Extraneal Peritoneal Dialysis Solution with 7.5% Icodextrin (HK-46627) from the market due to a potential quality issue.

The DH received notification from Baxter that complaints of leakage were received overseas with excessive liquid found in the over pouch of the product. Based on manufacturer's investigation, it was concluded that the problem was specific to the tubing used to manufacture the aforementioned batch of product. There is no similar complaint received in Hong Kong, however, leakage of a peritoneal solution bag might lead to contamination of the fluid inside. As a precautionary measure, Baxter is recalling the affected batch of the product from the market.

The above product, containing icodextrin and electrolytes, is a peritoneal dialysis solution. According to Baxter, the affected batch was all supplied to the Hospital Authority between February to March 2020. According to the Hospital Authority, most of the products of the affected batch have been used.

Patients who require use of the above product should seek advice from their healthcare professionals for appropriate arrangements. There are other batches of the product available on the market.

As on 7 December 2020, the DH has not received any adverse reaction report in connection with the affected product. A notice was posted on the Drug Office website on 20 November 2020 to alert the public of the product recall.

DH endorsed batch recall of Largactil 50mg ／ 2ml Solution for Injection

On 27 November 2020, the DH endorsed two licensed drug wholesalers, namely Sino-Asia Pharmaceutical Supplies Limited and Vantone Medical Supplies Co. Ltd., to recall one batch (batch number: A90142) of Largactil 50mg/2ml Solution for Injection from the market due to a potential quality issue.

The DH noticed from overseas drug regulatory agency that the manufacturer is recalling the affected batch due to an increased level of an impurity is found in the above batch of product. As a precautionary measure, the wholesalers voluntarily recall the affected batch of the product from the Hong Kong market.

The aforementioned product, containing chlorpromazine, is an antipsychotic prescription medicine. The product is not registered in Hong Kong but was imported for the treatment of particular patients by registered medical practitioners. According to the wholesalers, the affected batch has been supplied to the Hospital Authority and private hospitals.

Patients who require use of the above product should seek advice from their attending doctors if in doubt.

As on 7 December 2020, the DH has not received any adverse reaction reports in connection with the affected product. A notice was posted on the Drug Office website on 27 November 2020 to alert the public of the product recall.

Drug Incident

Two persons arrested for illegal sale of slimming product with undeclared drug ingredient

On 12 November 2020, the DH conducted an operation against the sale of a slimming product, namely KiMiSo Dark Chocolate, which was found to contain an undeclared drug ingredient. During the operation, a 59-year-old man and a 28-year-old woman were arrested by the Police for illegal sale of a Part 1 poison.

Acting upon intelligence, a sample of the above product was purchased via an Internet platform for analysis. The test result from the Government Laboratory revealed that the sample contained sibutramine, which is a banned drug ingredient.

Sibutramine is a Part 1 poison under the Pharmacy and Poisons Ordinance (Cap. 138) that was once used as an appetite suppressant. Since November 2010, pharmaceutical products containing sibutramine have been banned in Hong Kong because of an increased cardiovascular risk.

Weight control should be achieved through a balanced diet and appropriate exercise. The public should consult healthcare professionals before using any medication for weight control. They may visit the DH Drug Office's pages for health messages on weight control and slimming products and information on slimming products with undeclared Western drug ingredients.

Members of the public who have purchased the above product should stop consuming it immediately. They should consult healthcare professionals for advice if feeling unwell after consumption. Press release was posted on the Drug Office website on 12 November 2020 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.

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.

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

Update on Drug Office's website: You can now search the newly registered medicines in the past year at http://www.drugoffice.gov.hk/eps/drug/newsNRM60/en/healthcare_providers?pageNoRequested=1.

Details of ALL registered pharmaceutical products can still be found in the Drug Office website at http://www.drugoffice.gov.hk/eps/do/en/healthcare_providers/news_informations/reListRPP_index.html.

Useful Contact

Drug Complaint:

Tel: 2572 2068
Fax: 3904 1224
E-mail: pharmgeneral@dh.gov.hk

Adverse Drug Reaction (ADR) Reporting:

Tel: 2319 2920
Fax: 2319 6319
E-mail: adr@dh.gov.hk
Link: http://www.drugoffice.gov.hk/adr.html
Post: ***Undesirable Medical Advertisements and Adverse Drug Reaction Unit,***
Drug Office, Department of Health,
Suites 2002-05, 20/F, AIA Kowloon Tower,
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The purpose of Drug News is to provide healthcare professionals with a summary of local and overseas drug safety news released. Healthcare professionals are advised to keep update with the information and provide corresponding advice or therapeutic measure to patients and public.