Drug News
藥 物 情 報

Issue Number 170

This is a monthly digest of local and overseas drug safety news released by the Drug Office of the Department of Health in December 2023 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

European Union: PRAC recommends measures to minimise the risk of serious side effects with medicines containing pseudoephedrine

On 1 December 2023, the European Medicines Agency (EMA) announced that its safety committee, Pharmacovigilance Risk Assessment Committee (PRAC), had recommended new measures for medicines containing pseudoephedrine to minimise the risks of posterior reversible encephalopathy syndrome (PRES) and reversible cerebral vasoconstriction syndrome (RCVS). Pseudoephedrine is a stimulant that is often used as a decongestant in people who have a cold or allergies. PRES and RCVS are rare conditions that can involve reduced blood supply to the brain, potentially causing serious, life-threatening complications. With prompt diagnosis and treatment, symptoms of PRES and RCVS usually resolve.

Medicines containing pseudoephedrine are not to be used in patients with high blood pressure that is severe or uncontrolled (not being treated or resistant to treatment), or with severe acute (sudden) or chronic (long-term) kidney disease or failure.

Healthcare professionals should advise patients to stop using these medicines immediately and seek treatment if they develop symptoms of PRES or RCVS, such as severe headache with a sudden onset, feeling sick, vomiting, confusion, seizures and visual disturbances.

The PRAC's recommendations follow a review of all available evidence, including post-marketing safety data, which showed that pseudoephedrine is associated with risks of PRES and RCVS.

The product information for all pseudoephedrine-containing medicines will be updated to include the risks concerning PRES and RCVS and the new measures to be taken.

In Hong Kong, there are 102 registered pharmaceutical products containing pseudoephedrine. All products are pharmacy only medicines. As of the end of December 2023, the Department of Health (DH) had received 2 cases of adverse drug reaction with pseudoephedrine, but these cases were not related to PRES or RCVS. Related news was previously issued by EMA and MHRA, and was reported in Drug News Issue No. 160. In light of the above EMA's announcement, the DH issued letters to inform local healthcare professionals to draw their attention on 4 December 2023, and the matter will be discussed by the Registration Committee of the Pharmacy and Poisons Board.

European Union: GLP-1 receptor agonists' review: PRAC requests further clarifications from marketing authorisation holders

On 1 December 2023, the European Medicines Agency (EMA) announced that its safety committee, Pharmacovigilance Risk Assessment Committee (PRAC), had reviewed the available evidence from clinical trials, post-marketing surveillance and the published literature on reported cases of suicidal thoughts and thoughts of self-harm with medicines known as glucagon-like peptide-1 (GLP-1) receptor agonists (dulaglutide, exenatide, liraglutide, lixisenatide and semaglutide). While at this point no conclusion can be drawn on a causal association, there are several issues that still need to be clarified. The committee has agreed further lists of questions to be addressed by the respective marketing authorisation holders for these medicines, namely Ozempic, Rybelsus, Wegovy, Victoza, Saxenda, Xultophy, Byetta, Bydureon, Lyxumia,

Suliqua and Trulicity.

The PRAC will rediscuss this topic at its meeting in April 2024. EMA will communicate further when new information is available.

In Hong Kong, there are registered pharmaceutical products containing dulaglutide (4 products), exenatide (1 product), liraglutide (4 products), lixisenatide (2 products) and semaglutide (11 products). All products are prescription-only medicines. As of the end of December 2023, the Department of Health (DH) had received adverse drug reaction with dulaglutide (5 cases), exenatide (2 cases), liraglutide (1 case), lixisenatide (1 case) and semaglutide (3 cases), but these cases were not related to suicidal thoughts or self-injury. Related news was previously issued by European Medicines Agency and Health Sciences Authority, and was reported in Drug News Issue No. 165 and 167 respectively. As the safety review is ongoing, the DH will remain vigilant on the conclusion of the review and safety update of the drugs issued by other overseas drug regulatory authorities.

Australia: New warnings of romosozumab (Evenity) cardiovascular risks

On 7 December 2023, the Therapeutic Goods Administration (TGA) announced that its investigation into the risk of myocardial infarction and stroke in patients taking romosozumab (Evenity) found that stronger warnings regarding these risks were needed in the Product Information (PI) and Consumer Medicine Information (CMI). Romosozumab use is now also contraindicated in patients with a history of myocardial infarction or stroke.

TGA undertook a signal investigation in October 2023 to assess the risk of myocardial infarction and stroke with romosozumab. Myocardial infarction and stroke are serious life-threatening conditions that require prompt diagnosis and management. They can both result in death, permanent disability and significant hospital stays.

The Australian, European Union and United States product information documents all describe the results of 2 pivotal studies providing data about the potential risk of major adverse cardiac events associated with romosozumab. There was a higher rate of major adverse cardiac events (a composite of cardiovascular death, non-fatal myocardial infarction and non-fatal stroke) associated with romosozumab in one trial but not the other. The disparity between these 2 trials has been a focus for regulators assessing the safety of this medicine.

TGA considers that the benefit-risk balance of romosozumab remains positive, and it continues to be a useful treatment for osteoporosis for some patients.

The following sections of the PI and CMI have been updated to reflect an increased risk of myocardial infarction and stroke: Contraindications; Special warning and precautions for use; and Adverse events.

Health professionals should be alert to the updated warnings and new contraindications and should inform patients and carers of the potential cardiovascular risks associated with romosozumab use.

A search of TGA's Database of Adverse Event Notifications on 27 November 2023 identified 9 related distinct case reports (some including multiple adverse events): intraventricular haemorrhage (2), cerebrovascular accident (2), acute myocardial infarction (1), cerebral haemorrhage (1), embolic stroke (1), myocardial infarction (2), transient ischaemic attack (1). The outcomes of the reported adverse events were all serious with 2 leading to death.

In Hong Kong, there is one registered pharmaceutical product containing romosozumab, namely Evenity Solution For Injection in Prefilled Syringe 105mg/1.17ml (HK-66741). The product is registered by Amgen Hong Kong Limited. It is a prescription-only medicine. As of the end of December 2023, the Department of Health (DH) had received 2 cases of adverse drug reaction related to romosozumab, but these cases were not related to myocardial infarction or stroke. The current product information of the locally registered Evenity product includes safety information on the risk of myocardial infarction and stroke, and the product is contraindicated in patients with a history of myocardial infarction or stroke. The DH will remain vigilant on safety update of the drug issued by other overseas drug regulatory authorities.

European Union: EMA confirms recommendation for non-renewal of authorisation of multiple myeolma medicine Blenrep (belantamab mafodotin)

On 15 December 2023, the European Medicines Agency (EMA) announced that its human medicines committee (CHMP) had confirmed its initial recommendation to not renew the conditional marketing authorisation for Blenrep (belantamab mafodotin) because recent data did not confirm its effectiveness; the benefits of Blenrep are therefore considered to no longer outweigh its risks.

Blenrep is a medicine for treating multiple myeloma (a cancer of the bone marrow). It was authorised for adults who had received at least four previous treatments and whose disease did not respond to certain other types of treatment and had worsened since the last treatment. During a re-examination requested by the company that markets the medicine, the CHMP re-assessed the results from the DREAMM-3 study, which compared Blenrep with pomalidomide plus low-dose dexamethasone.

The study did not find that patients who received Blenrep lived longer without their disease getting worse when compared with patients who received pomalidomide plus dexamethasone. As confirming this progression-free survival was a requirement at the time of Blenrep's initial authorisation, the Committee concluded that the data did not confirm the medicine's benefits and recommended not renewing its authorisation.

During the re-examination, the CHMP consulted a scientific advisory group (SAG) comprising of experts in the treatment of cancer. These experts were of the view that the DREAMM-3 study did not confirm the effectiveness of Blenrep. However, the majority of SAG experts were also of the opinion that Blenrep could be a treatment option for some patients for whom other treatments were not suitable.

In reaching its final opinion, the CHMP considered the views of the SAG, the results of the DREAMM-3 study which failed to confirm the effectiveness of Blenrep, and the medicine's safety profile. All these considerations informed the CHMP's conclusion that the benefits of Blenrep no longer outweigh its risks and its recommendation not to renew the medicine's conditional marketing authorisation.

Information for patients:

- EMA has recommended not renewing the marketing authorisation for the cancer medicine Blenrep. Once this recommendation is confirmed by the European Commission, Blenrep will no longer be authorised in the EU. However, the company may still supply the medicine through compassionate use or named-patient programmes to patients already receiving Blenrep.
- Blenrep was approved to treat multiple myeloma. As data were limited at the time of authorisation, the medicine was approved on the condition that the company carried out a study to confirm its effectiveness.
- The DREAMM-3 study failed to show that patients treated with Blenrep lived longer without their disease getting worse compared with those treated with pomalidomide and low-dose dexamethasone, another authorised treatment for multiple myeloma.
- As the medicine's effectiveness could not be confirmed, EMA concluded that the benefits of Blenrep are considered to no longer outweigh its risks.
- If you are receiving Blenrep, you should speak to your doctor about this decision and what it means for you and your treatment.

Information for healthcare professionals:

- EMA has recommended not to renew the conditional marketing authorisation for Blenrep, because recent data did not confirm its effectiveness; the benefits of Blenrep are therefore considered to no longer outweigh its risks.
- Once this recommendation is confirmed by the European Commission, Blenrep will no longer be authorised in the EU. However, the company may still supply the medicine through compassionate use or named-patient programmes to existing patients.
- Healthcare professionals should not start any new patients on Blenrep.
- Blenrep received a conditional marketing authorisation in August 2020; the marketing authorisation was subject to annual renewals based on the results of additional studies imposed on the marketing authorisation holder.
- The recent DREAMM-3 study failed to show that patients treated with Blenrep lived longer without disease progression than those treated with pomalidomide and low-dose dexamethasone.

- This phase 3, open-label, randomised (2:1) study compared Blenrep with pomalidomide and low-dose dexamethasone in 325 patients with relapsed/refractory multiple myeloma. The primary endpoint agreed as part of the specific obligation was superiority in investigator-assessed progression-free survival (PFS). The study found no statistically significant difference in PFS between the two groups (HR 1.03; 95% confidence interval: 0.72, 1.47).

In Hong Kong, there is one registered pharmaceutical product containing belantamab mafodotin, namely Blenrep Powder For Concentrate For Solution For Infusion 100mg (HK-67213) registered by GlaxoSmithKline Limited, and is a prescription-only medicine. Related news on non-renewal of authorization of multiple myeloma medicine Blenrep was previously issued by EMA, and was reported in Drug News Issue No. 167. The Department of Health (DH) issued letters to inform local healthcare professionals to draw their attention on 18 September 2023. In September 2023, the Registration Committee of the Pharmacy and Poisons Board discussed the matter, and decided to keep vigilant on any update from EMA and any change in worldwide marketing authorization.

In light of the above EMA's announcement, the matter will be further discussed by the Registration Committee of the Pharmacy and Poisons Board.

Singapore: HSA: Isotretinoin and risk of psychiatric disorders and sexual dysfunction

On 15 December 2023, the Health Sciences Authority (HAS) announced a safety alert on isotretinoin and risk of psychiatric disorders and sexual dysfunction. Isotretinoin is a systemic oral retinoid that has been registered in Singapore since 1990. Currently, there are four brands registered, namely Acnotin (Goldplus Universal Pte Ltd), Nimegen (Zyfas Pharma Pte Ltd), Oratane (Apex Pharma Marketing Pte Ltd) and Roaccutane (Roche Singapore Pte Ltd) in Singapore. It is indicated for the treatment of severe forms of acne (nodulo-cystic forms) and acne which has failed to respond to other therapies. The use of isotretinoin in paediatric patients less than 12 years of age has not been studied. Careful consideration should be given to patients aged 12 to 17 years who are being treated for severe recalcitrant nodular acne, especially for those with known metabolic or structural bone disease.

Psychiatric disorders and sexual dysfunction have previously been reported with the use of isotretinoin. HSA had reviewed the evidence on these associations in 2018 and 2017, respectively, and concluded that a definitive causal relationship could not be established due to limitations in the available data then. Nevertheless, as the role of isotretinoin in the development of psychiatric and sexual adverse events could not be ruled out, the local package inserts (PI) of isotretinoin products in Singapore had been strengthened to include safety information on both risks.

Since HSA's last review, new information has emerged, including published literature and actions taken by international drug regulatory agencies. This led HSA to re-evaluate whether the existing safety measures should be further strengthened. Based on the current available information, HSA, in consultation with its Product Vigilance Advisory Committee (PVAC), has concluded that the benefit-risk profile of isotretinoin remains favourable for its approved indications and the current product labelling is sufficient to mitigate both safety concerns.

In 2019, the UK Medicines and Healthcare products Regulatory Agency's (MHRA) advisory committee, the Commission on Human Medicines (CHM), endorsed an independent review by the Isotretinoin Expert Working Group (IEWG) to address concerns raised by patients, families, and other stakeholders regarding the potential adverse effects of isotretinoin on mental health and sexual function when used for acne treatment. The review aimed to evaluate the impact of these adverse effects on the balance of benefits and risks of isotretinoin treatment. The CHM's review findings were published in April 2023, and their recommendations included warnings on the potential risk of psychiatric and sexual disorders and the need of patient counselling in isotretinoin product labels, improvement in their assessment and monitoring, and additional oversight of treatment initiation for patients under 18 years old. These new safety measures and supporting materials were implemented by the UK MHRA on 31 October 2023, and healthcare professionals were advised to integrate them into their clinical practice to strengthen the safe use of isotretinoin.

Other international drug regulatory agencies, namely, US Food and Drug Administration (FDA),

European Medicines Agency (EMA), Health Canada, Australia Therapeutic Goods Administration (TGA), had also previously reviewed the risks of psychiatric disorders and sexual dysfunction with isotretinoin between 2016 to 2018, and most of them had not imposed safety measures beyond product information labelling to mitigate these risks. At present, no additional safety measures have been implemented by these agencies in response to the UK MHRA's regulatory actions.

Based on the sales data in Singapore, the estimated patient exposure to isotretinoin has remained relatively stable between January 2019 and June 2023, ranging from approximately 3,500 to 4,500 patient-years. Given its long history of use in the local market, there were few local reports of suspected psychiatric disorders and sexual dysfunction associated with isotretinoin. Of the 65 local adverse event reports received for isotretinoin between 1999 to 2023 in Singapore, three were related to psychiatric disorders (depression, psychotic disorder, and suicidal ideation), while one reported erectile dysfunction. These reports generally had limited information or were confounded by the patients' medical history which precluded a meaningful causality assessment. However, HSA cannot rule out the possibility of under-reporting of these adverse events.

The local PIs of isotretinoin products in Singapore currently already contain warnings on psychiatric disorders such as depression, anxiety, mood alterations, psychotic disorders and suicidal ideation. Sexual dysfunction, including erectile dysfunction and decreased libido, are also listed in the local PI as adverse events reported in the post-market setting. Patient educational materials for isotretinoin are available on publicly accessible platforms, including the Medication Information Leaflets (MILs) on HealthHub. These MILs provide a brief overview on the administration of isotretinoin and its potential adverse effects. They have highlighted the rare but serious adverse effect of mood changes including depression which require immediate medical advice.

HSA, in consultation with its PVAC, has assessed that the benefit-risk profile of isotretinoin remains favourable and the warnings and safety information in the local PIs of isotretinoin products are sufficient to manage the risks of psychiatric disorders and sexual dysfunction. Nevertheless, it would be relevant to remind healthcare professionals who are prescribing isotretinoin of these potential risks and the relevant measures to be taken.

To allow for prompt detection and management of these adverse effects, healthcare professionals may wish to consider counselling and screening their patients for depressive symptoms or other psychiatric adverse effects when prescribing isotretinoin. They may also consider referring their patients to the relevant specialists for further assessment, if necessary. Healthcare professionals may refer to the available MILs on isotretinoin during medication counselling to facilitate the communication of isotretinoin use and its adverse effects to patients and/or their caregivers.

In Hong Kong, there are 11 registered pharmaceutical products containing isotretinoin. All products are prescription-only medicines. As of the end of December 2023, the Department of Health (DH) had received 2 cases of adverse drug reaction related to isotretinoin, but these cases were not related to mental health or sexual function side effects. Related news was previously issued by MHRA, and was reported in the Drug News since Issue No. 96, with the latest update reported in Drug News Issue No. 168. The DH issued letters to inform local healthcare professionals to draw their attention on 27 October 2017 and 27 April 2023.

Currently, the sales pack or package insert of locally registered isotretinoin-containing products should include warnings on suicide, suicidal attempts and sexual dysfunction including erectile dysfunction and decreased libido. As previously reported, the matter will be discussed by the Registration Committee of the Pharmacy and Poisons Board.

The United States: FDA approves safety labeling changes for opioid pain medicines

On 15 December 2023, the US Food and Drug Administration (FDA) announced final approval and implementation of required labeling updates to continue efforts to address the evolving opioid crisis, and to urge health care professionals to take a more patient-centered approach when prescribing opioid analgesic products.

In April 2023, FDA notified application holders of New Drug Applications and Abbreviated New Drug Applications of required safety labeling updates needed for immediate-release (IR) and extended-release/long-acting (ER/LA) opioid

analgesics. The required safety labeling updates, originally listed in an April 2023 Drug Safety Communication, include the addition of language stating:

- the risk of overdose increases as the dosage increases for all opioid pain medicines;
- IR opioids should not be used for an extended period of time unless a patient's pain remains severe enough to require them and alternative treatment options continue to be inadequate;
- many acute pain conditions treated in the outpatient setting require no more than a few days of an opioid pain medicine; and
- it is recommended to reserve ER/LA opioid pain medicines for severe and persistent pain that requires an extended treatment period with a daily opioid pain medicine and for which alternative treatment options are inadequate.

The required updates also include a new warning about opioid-induced hyperalgesia (OIH), a condition in which opioid use causes an increase in pain (hyperalgesia) or an increased sensitivity to pain (allodynia). The warning also includes information on differentiating OIH symptoms from those of opioid tolerance and withdrawal.

FDA's approval of these labeling updates is a testament to the agency's continuing progress towards implementing the FDA Overdose Prevention Framework, which provides its vision to undertake impactful, creative actions to prevent drug overdoses and reduce deaths.

In Hong Kong, there are registered pharmaceutical products containing buprenorphine (4 products), codeine (353 products), fentanyl (16 products), morphine (15 products), oxycodone (14 products) and tramadol (42 products). These products are pharmacy-only medicines or prescription-only medicines. There is no registered pharmaceutical product containing hydrocodone, hydromorphone and oxymorphone. While the FDA's announcement did not highlight any specific adverse event, as of the end of December 2023, the Department of Health (DH) had received adverse drug reaction related to codeine (4 cases), fentanyl (6 cases), morphine (11 cases), oxycodone (2 cases) and tramadol (9 cases). The DH had not received any case of adverse drug reaction related to buprenorphine.

Related news on the safe and appropriate use of opioid analgesics was previously issued by various overseas drug regulatory authorities, and was reported in the Drug News since Issue No. 47, with the latest update reported in Drug News Issue No. 162. The DH issued letters to inform local healthcare professionals to draw their attention on 11 September 2013 and 14 April 2023. In February 2015, the Registration Committee of the Pharmacy and Poisons Board discussed the matter, and decided that pharmaceutical products which are controlled-release, extended-release or long-acting opioid analgesics (containing hydromorphone, morphine, oxycodone, oxymorphone, tapentadol, fentanyl, buprenorphine and methadone) should include safety information about the risks of addiction, abuse, misuse, overdose and death, and limitations of use in patients with severe pain for which alternative treatment options are inadequate.

The risks of tolerance, dependence, withdrawal symptoms and respiratory depression associated with the use of opioid analgesics, and the risks associated with using opioid analgesics in conjunction with benzodiazepines or other medicines that depress the central nervous system are documented in overseas reputable drug references such as the "Martindale: The Complete Drug Reference" and "AHFS Drug Information". The DH will remain vigilant on safety update of the drugs issued by other overseas drug regulatory authorities for consideration of any action deemed necessary.

The United Kingdom: Aripiprazole (Abilify and generic brands): risk of pathological gambling

On 18 December 2023, the Medicines and Healthcare products Regulatory Agency (MHRA) announced that healthcare professionals prescribing aripiprazole are reminded to be alert to the risk of addictive gambling and other impulse control disorders.

Aripiprazole belongs to a class of medicines called antipsychotics. The MHRA has received reports from stakeholders raising concerns about a lack of awareness of the association between aripiprazole and the development or worsening of addictive gambling behaviours. Since the beginning of 2023, there has been an increased number of Yellow Card reports for aripiprazole which include gambling, gambling disorder or obsessive-compulsive disorder.

A review of the available evidence was considered by the Neurology, Pain and Psychiatry expert

advisory group (NPPEAG) of the Commission on Human Medicines. The NPPEAG noted that the Summary of Product Characteristics (SmPC) and the Patient Information Leaflet (PIL) for aripiprazole contain information regarding pathological gambling and other impulse control disorders. The SmPC states that impulse control disorders may result in harm to the patient and others if not recognised and advises consideration of dose reduction or stopping the medication if a patient develops increased urges while taking aripiprazole. In reviewing this issue, the NPPEAG recommended that the MHRA reminds healthcare professionals and patients of these risks.

From 30 June 2009 to 28 August 2023, the MHRA received 69 Yellow Card reports citing aripiprazole as a suspect medicine for side effects of gambling or gambling disorder. Thirty-two of these reports were received in 2023. Fourteen reports were also received describing obsessive-compulsive disorders, or related symptoms, with aripiprazole. Aripiprazole is a frequently prescribed antipsychotic medication and usage has been steadily increasing over the past four years. It is not possible to determine the frequency of these side effects from the currently available data.

Across the 69 reports of gambling and gambling disorder, most reports concerned people aged 20 to 40 years, although there were reports in patients up to 60 years of age. In many cases the patients had no previous history of gambling behaviour. Eight of the cases described patients who had lost significant sums of money and accrued considerable debts. In the majority of cases, cessation of aripiprazole led to a marked reduction or total loss of impulses to gamble. Several of the cases mention that the patient was not aware of this side effect. Awareness of this risk must increase among patients and prescribers, as gambling is recognised as a common risk factor linked to suicide and is included within the suicide prevention in England: 5-year cross sector strategy.

Advice for healthcare professionals:

- There has been an increase in the number of Yellow Card reports of gambling disorder and pathological gambling associated with aripiprazole use; concerns have also been raised about a lack of awareness of this issue.
- The United Kingdom reports occurred in patients with and without a prior history of gambling disorder and the majority were reported to resolve upon reduction of dose or stopping treatment with aripiprazole.
- Advise patients and their caregivers to be alert to the development of new or increased urges to gamble and other impulse control symptoms, such as excessive eating or spending, or an abnormally high sex drive.
- Consider dose reduction or stopping the medication if a patient develops these symptoms.
- Awareness of this risk must increase among patients and prescribers, as gambling is recognised as a common risk factor linked to suicide and is included within the suicide prevention in England: 5-year cross sector strategy.

In Hong Kong, there are 33 registered pharmaceutical products containing aripiprazole. All products are prescription-only medicines. As of the end of December 2023, the Department of Health (DH) had received one case of adverse drug reaction related to aripiprazole, but this case was not related to pathological gambling.

Related news was previously issued by Health Canada and the United States Food and Drug Administration, and was reported in Drug News Issue No. 73. The DH issued letters to inform local healthcare professionals to draw their attention on 3 November 2015. In December 2016, the Registration Committee of the Pharmacy and Poisons Board discussed the matter, and decided that the product information of locally registered aripiprazole-containing products should include safety information on the risk of pathological gambling and other compulsive behaviours. The DH will remain vigilant on safety update of the drug issued by other overseas drug regulatory authorities.

The United Kingdom: Vitamin B12 (hydroxocobalamin, cyanocobalamin): advise patients with known cobalt allergy to be vigilant for sensitivity reactions

On 18 December 2023, the Medicines and Healthcare products Regulatory Agency (MHRA) announced that there are case reports in the literature describing cobalt sensitivity-type reactions in patients being treated for vitamin B12 deficiency.

Hydroxocobalamin and cyanocobalamin are oral and injectable forms of vitamin B12 that are used to treat vitamin B12 deficiency. Endogenous

vitamin B12 and these medicines contain a cobalt component. The MHRA received a query from a member of the public, as part of a report to the Yellow Card scheme of a suspected reaction associated with vitamin B12 treatment and cobalt allergy. As a result of this, the MHRA conducted a review of this topic.

There is evidence within the literature of cobalt sensitivity reactions occurring following administration of vitamin B12. Additionally, the MHRA received three Yellow Card reports including the case described above, which report vitamin B12 as a suspect drug and possible allergic reactions to cobalt. Following the MHRA's review, it was considered appropriate to improve awareness that hydroxocobalamin and cyanocobalamin medicines contain cobalt.

The MHRA has subsequently requested relevant Marketing Authorisation Holders (MAHs) to update the Summary of Product Characteristics (SmPC) to include that vitamin B12 contains cobalt. The MHRA has also requested MAHs to update the Patient Information Leaflet (PIL) to advise patients that cobalt is contained within vitamin B12 and that they should talk to a healthcare professional if they have a known cobalt allergy.

Patients with a cobalt sensitivity may present with cutaneous symptoms such as chronic or subacute allergic contact dermatitis. Cobalt allergy may also trigger an erythema multiforme-like eruption. The hypersensitivity reaction may be immediate or delayed to 12 to 72 hours following exposure. Additional vigilance may be required beyond this time period.

There is no alternative treatment for vitamin B12 deficiency, therefore, vitamin B12 use is not contraindicated in patients with cobalt allergy that presents only as cutaneous symptoms. However, where previous serious allergic reaction is established in known cobalt allergy patients, individual assessment of the benefits and risks should be conducted before starting treatment.

Hydroxocobalamin products which are indicated in the treatment of known or suspected cyanide poisoning are excluded from these precautions, considering it is a medical emergency in which the potentially life-saving benefit of treatment would outweigh the risk of allergic reaction.

Patients and carers should be reminded about the symptoms of cobalt sensitivity and to seek medical advice if they experience these symptoms. Symptoms should be monitored and treated as clinically appropriate.

Advice for healthcare professionals:

- Cobalt sensitivity reactions typically present with cutaneous symptoms of chronic or subacute allergic contact dermatitis. Infrequently, cobalt allergy may trigger an erythema multiforme-like reaction. Symptom onset may be immediate or delayed up to 72 hours post-administration.
- Cobalt allergy is estimated to affect 1 to 3% of the general population.
- If cobalt sensitivity-type reactions occur, assess the individual benefits and risks of continuing treatment and, if necessary to continue, advise patients on appropriate management of symptoms.

In Hong Kong, there are registered pharmaceutical products for human use which contain vitamin B12 substances in oral and injectable forms, including hydroxocobalamin (4 products), cyanocobalamin (73 products) and mecobalamin (5 products). Two of these products contain both hydroxocobalamin and cyanocobalamin. As of the end of December 2023, the Department of Health (DH) had received one case of adverse drug reaction related to cyanocobalamin, but this case was not related to cobalt sensitivity. The DH had not received any case of adverse drug reaction related to hydroxocobalamin or mecobalamin. In light of the above MHRA's announcement, the DH issued letters to inform local healthcare professionals to draw their attention on 19 December 2023, and the matter will be discussed by the Registration Committee of the Pharmacy and Poisons Board.

Drug Incident

Public urged not to buy or consume slimming products with undeclared controlled and banned drug ingredients

On 8 December 2023, the Department of Health (DH) appealed to the public not to buy or consume a slimming product, namely "simple heart SPECIFIC SLIMMING PRODUCT", as it was found to contain undeclared controlled and banned drug ingredients.

Acting upon a public complaint, the DH obtained sample of the above product via a social media platform for analysis. Test results from the Government Laboratory revealed that the sample contained sibutramine, N-desmethylsibutramine and frusemide which are all Part 1 poisons under the Pharmacy and Poisons Ordinance (Cap. 138). The DH's investigation is continuing.

Sibutramine 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. N-desmethylsibutramine is a substance structurally similar to sibutramine. Frusemide is a diuretic used in the treatment of high blood pressure, heart failure and oedema. Common adverse effects include feeling thirsty, dizziness, headaches and fast or irregular heartbeat.

A press release was posted in the Drug Office website on 8 December 2023 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 $50,000 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: Adverse Drug Reaction and Adverse Event Following Immunization Unit,
Drug Office, Department of Health,
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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.