# Drug News
# 藥 物 情 報

**Issue Number 171**

***This is a monthly digest of local and overseas drug safety news released by the Drug Office of the Department of Health in January 2024 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

**The United States: Update on FDA's ongoing evaluation of reports of suicidal thoughts or actions in patients taking a certain type of medicines approved for type 2 diabetes and obesity: glucagon-like peptide-1 receptor agonists**

On 11 January 2024, the US Food and Drug Administration (FDA) announced that it has been evaluating reports of suicidal thoughts or actions in patients treated with a class of medicines called glucagon-like peptide-1 receptor agonists (GLP-1 RAs). These medicines are used to treat people with type 2 diabetes or to help those with obesity or overweight to lose weight. FDA's preliminary evaluation has not found evidence that use of these medicines causes suicidal thoughts or actions. FDA-approved GLP-1 RAs include exenatide, liraglutide, dulaglutide, lixisenatide, semaglutide and tirzepatide.

Over the last several months, FDA has conducted detailed reviews of reports of suicidal thoughts or actions received in the FDA Adverse Event Reporting System. Because the information provided was often limited and because these events can be influenced by other potential factors, FDA determined that the information in these reports did not demonstrate a clear relationship with the use of GLP-1 RAs. Similarly, FDA's reviews of the clinical trials, including large outcome studies and observational studies, did not find an association between use of GLP-1 RAs and the occurrence of suicidal thoughts or actions. However, because of the small number of suicidal thoughts or actions observed in both people using GLP-1 RAs and in the comparative control groups, FDA cannot definitively rule out that a small risk may exist; therefore, FDA is continuing to look into this issue.

Additional evaluations include a meta-analysis of clinical trials across all GLP-1 RA products and an analysis of postmarketing data in the Sentinel System. A meta-analysis is a large, combined analysis of findings from clinical trials. Sentinel is a very large data network that contains health insurance claims and patient health records that can be used to investigate safety questions about FDA-regulated products. FDA will communicate the final conclusions and recommendations after FDA completes the review or has more information to share.

Patients should not stop taking GLP-1 RAs without first consulting their healthcare professional, as stopping these medicines may worsen their condition. Talk to their healthcare professional if they have questions or concerns. Tell their healthcare professional if they experience new or worsening depression, suicidal thoughts, or any unusual changes in mood or behavior.

Healthcare professionals should monitor for and advise patients using GLP-1 RAs to report new or worsening depression, suicidal thoughts, or any unusual changes in mood or behavior. Healthcare professionals should consult the prescribing information when treating patients with these medications.

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. There is no registered pharmaceutical product containing tirzepatide. As of the end of January 2024, the Department of Health (DH) had received adverse drug reaction related to dulaglutide (5 cases), exenatide (2 cases), liraglutide (1 case), lixisenatide (1 case) and semaglutide (4 cases), but

these cases were not related to suicidal thoughts or actions. Related news was previously issued by European Medicines Agency and Singapore Health Sciences Authority, and was reported in Drug News Issue No. 165, 167 and 170. 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.

**The United States: FDA adds Boxed Warning for increased risk of severe hypocalcemia in patients with advanced chronic kidney disease taking osteoporosis medicine Prolia (denosumab)**

On 19 January 2024, the US Food and Drug Administration (FDA) announced that based on a completed review of available information, it was concluded that the osteoporosis medicine Prolia (denosumab) increases the risk of severe hypocalcemia, very low blood calcium levels, in patients with advanced chronic kidney disease (CKD), particularly patients on dialysis. Severe hypocalcemia appears to be more common in patients with CKD who also have a condition known as mineral and bone disorder (CKD-MBD). In patients with advanced CKD taking Prolia, severe hypocalcemia resulted in serious harm, including hospitalization, life-threatening events, and death. As a result, FDA is revising the Prolia prescribing information to include a new Boxed Warning, its most prominent warning, communicating this increased risk.

FDA is adding a Boxed Warning to the Prolia prescribing information about the significant risk of developing severe hypocalcemia in patients with advanced CKD. This warning and new labeling contains information to help reduce this risk, including appropriate patient selection for Prolia treatment, increased monitoring of blood calcium levels, and other strategies. FDA is also adding this updated information to the patient Medication Guide and the Prolia Risk Evaluation and Mitigation Strategy (REMS), a drug safety program required by FDA to help ensure that Prolia's benefits outweigh its risks.

It is important that the appropriateness of Prolia treatment in patients with advanced CKD be determined by a health care professional with expertise in the diagnosis and management of CKD-MBD including renal osteodystrophy, a complication that weakens bone. Treating bone disease in patients with advanced and dialysis-dependent CKD is challenging because of the difficulty in diagnosing and confirming the underlying altered bone metabolism responsible for the low bone mass and increased fracture risk, and the complex benefit-risk considerations of approved osteoporosis treatments in this population.

Before prescribing Prolia, health care professionals should assess their patients' kidney function. For patients with advanced CKD, particularly those on dialysis, health care professionals should consider the risk of severe hypocalcemia with Prolia in the context of other available treatments for osteoporosis. If Prolia is still being considered for these patients, for initial or continued use, check their calcium blood levels and assess them for evidence of CKD-MBD.

Treatment with Prolia in patients with advanced CKD, including those on dialysis, and particularly patients with diagnosed CKD-MBD should involve a health care provider with expertise in the diagnosis and management of CKD-MBD. Proper management of CKD-MBD, correction of hypocalcemia, and supplementation with calcium and activated vitamin D prior to Prolia treatment is expected to decrease the risk of developing severe hypocalcemia and any associated complications. Following Prolia administration, close monitoring of blood calcium levels and prompt management of hypocalcemia is essential to prevent complications such as seizures or arrhythmias. Advise patients to promptly report symptoms that could be consistent with hypocalcemia.

In Hong Kong, Prolia Solution For Injection In Pre-filled Syringe 60mg/ml (USA) (HK-60588) is a pharmaceutical product containing 60mg of denosumab which is registered by Amgen Hong Kong Limited. The product is a prescription-only medicine. As of the end of January 2024, the Department of Health (DH) had received 64 cases of adverse drug reaction related to denosumab, of which 3 cases were related to hypocalcemia/serum calcium decreased. Related news on the risk of hypocalcemia associated with the use of Xgeva (containing 120mg of denosumab) and Prolia was previously issued by Health Canada, Singapore Health Sciences Authority and US FDA, and was reported in Drug News Issue No. 31, 59 and 157. The DH issued letters to inform local healthcare professionals to draw their attention on 1 June 2012. In December 2012, the Registration

Committee of the Pharmacy and Poisons Board discussed the matter for Xgeva and Prolia, and the sales pack label and/or package insert of denosumab products have included safety information about the risk of hypocalcemia (including in patients with severe renal impairment or receiving dialysis). The DH will remain vigilant on safety update of the drug issued by other overseas drug regulatory authorities for consideration of any action deemed necessary.

**The United Kingdom: Fluoroquinolone antibiotics: must now only be prescribed when other commonly recommended antibiotics are inappropriate**

On 22 January 2024, the Medicines and Healthcare products Regulatory Agency (MHRA) announced that systemic fluoroquinolones must now only be prescribed when other commonly recommended antibiotics are inappropriate. This follows a review by the MHRA which looked at the effectiveness of current measures to reduce the identified risk of disabling and potentially long-lasting or irreversible side effects.

Systemic and inhaled fluoroquinolones are associated with a risk of serious, disabling, long-lasting and potentially irreversible adverse reactions, estimated to occur in at least between 1 and 10 people in every 10,000 who take a fluoroquinolone. These may affect multiple body systems and include musculoskeletal, nervous, psychiatric and sensory reactions. These adverse reactions have been reported in patients irrespective of their age and potential risk factors.

Patients have reported that experiencing long-lasting or disabling reactions can affect their mental health, particularly when they perceive healthcare professionals fail to adequately acknowledge the reactions or the possibility that they are associated with a fluoroquinolone. Tendon damage can occur within 48 hours of commencing treatment, or the effects can be delayed for several months and become apparent after stopping treatment.

There are no proven drug treatments for these side effects. However, it is important that fluoroquinolones are stopped immediately at the first signs of a musculoskeletal, neurological or psychiatric side effect to avoid further exposure, which could potentially worsen adverse reactions. These symptoms should be appropriately investigated.

Restrictions to the use of fluoroquinolones were introduced in 2019 to minimise the risk of these reactions. The MHRA has reviewed the effectiveness of these measures in the United Kingdom and sought the advice of the Commission on Human Medicines. As a result of this review a reminder about these risks was published in August 2023.

The MHRA has now taken additional regulatory action to update the indications for all systemic fluoroquinolones to state they should only be used when other commonly recommended antibiotics are inappropriate. Situations where other antibiotics are considered to be inappropriate are where:

- There is resistance to other first-line antibiotics recommended for the infection.
- Other first-line antibiotics are contraindicated in an individual patient.
- Other first-line antibiotics have caused side effects in the patient requiring treatment to be stopped.
- Treatment with other first-line antibiotics has failed.

The description of disabling and potentially long-lasting or irreversible side effects in the safety information has also been updated, to include more detail about the range of psychiatric symptoms that may occur as part of these reactions. These may include sleep disorders, anxiety, panic attacks, confusion or depression. While the frequency of disabling and potentially long-lasting or irreversible side effects cannot be estimated precisely using available data, the updated reporting incidence indicates a minimum frequency of between 1 and 10 per 10,000 patients.

Advice for healthcare professionals:

- Systemic (by mouth, injection, or inhalation) fluoroquinolones can cause long-lasting (up to months or years), disabling and potentially irreversible side effects, sometimes affecting multiple body systems and senses.
- The United Kingdom indications for systemic fluoroquinolones have been updated so they must only be used in situations when other antibiotics, that are commonly recommended for the infection, are inappropriate.
- Situations in which other antibiotics are considered to be inappropriate and where a fluoroquinolone may be indicated are where: there is resistance to other first-line antibiotics recommended for the infection; other first-line antibiotics are contraindicated in an individual

patient; other first-line antibiotics have caused side effects in the patient requiring treatment to be stopped; treatment with other first-line antibiotics has failed.

- This goes further than previous measures which set out that fluoroquinolones should not be prescribed for non-severe or self-limiting infections, or non-bacterial conditions, for example, non-bacterial (chronic) prostatitis. These measures are still in place.
- As a reminder, patients should be advised to stop fluoroquinolone treatment at the first signs of a serious adverse reaction, such as tendinitis or tendon rupture, muscle pain, muscle weakness, joint pain, joint swelling, peripheral neuropathy and central nervous system effects, and to contact their doctor immediately.
- Remain alert to the risk of suicidal thoughts and behaviours with use of fluoroquinolone antibiotics. A reminder about these risks was published in September 2023.
- As a reminder of advice published in August 2023: avoid fluoroquinolone use in patients who have previously had serious adverse reactions with a quinolone antibiotic (for example, nalidixic acid) or a fluoroquinolone antibiotic; prescribe fluoroquinolones with special caution for people older than 60 years and for those with renal impairment or solid-organ transplants, because they are at a higher risk of tendon injury; avoid coadministration of a corticosteroid with a fluoroquinolone since this could exacerbate fluoroquinolone-induced tendinitis and tendon rupture.

In Hong Kong, there are registered pharmaceutical products containing systemic fluoroquinolones for use in human, including ciprofloxacin (51 products), levofloxacin (44 products), moxifloxacin (6 products), norfloxacin (3 products), ofloxacin (14 products) and prulifloxacin (one product). All products are prescription-only medicines.

As of the end of January 2024, the Department of Health (DH) had received adverse drug reaction with regard to levofloxacin (13 cases; of which 3 cases were reported as musculoskeletal, nervous and/or psychiatric reactions) and ofloxacin (4 cases; all of these cases were reported as attempted suicide/completed suicide). The DH had received adverse drug reaction related to ciprofloxacin (one case) and moxifloxacin (one case), but these cases were not related to the disabling side effects mentioned in the above MHRA's announcement. The DH had not received any case of adverse drug reaction related to norfloxacin and prulifloxacin.

Related news on the risk of musculoskeletal, nervous and psychiatric adverse reactions associated with the use of fluoroquinolones was previously issued by various overseas drug regulatory authorities, and was reported in the Drug News since Issue No. 25, with the latest update reported in Drug News Issue No. 167. The Department of Health (DH) issued letters to inform local healthcare professionals to draw their attention on 8 November 2011, 16 August 2013, 13 May 2016, 11 July 2018 and 8 October 2018.

In June 2019, the Registration Committee of the Pharmacy and Poisons Board discussed the matter, and decided that the sales pack labels and/or package inserts of locally registered pharmaceutical products containing fluoroquinolones for systemic use should contain safety information about the risk of disabling and potentially irreversible serious adverse reactions (including tendinitis and tendon rupture, peripheral neuropathy and central nervous system effects).

In light of the above MHRA's announcement, the Department of Health (DH) issued letters to inform local healthcare professionals to draw their attention on 23 January 2024, and the matter will be discussed by the Registration Committee of the Pharmacy and Poisons Board.

**The United Kingdom: Omega-3-acid ethyl ester medicines (Omacor/Teromeg 1000mg capsules): dose-dependent increased risk of atrial fibrillation in patients with established cardiovascular diseases or cardiovascular risk factors**

On 22 January 2024, the Medicines and Healthcare products Regulatory Agency (MHRA) announced that systematic reviews and meta-analyses of randomised controlled trials have highlighted a dose-dependent increased risk of atrial fibrillation in patients with established cardiovascular diseases or cardiovascular risk factors treated with omega-3-acid ethyl ester medicines compared to placebo.

A recent European regulatory review recommended "atrial fibrillation" should be listed as a common adverse reaction (may affect up to 1 in 10 people)

in the product information of medicines containing omega-3-acid ethyl esters. The review of safety and efficacy data for omega-3-acid ethyl ester medicines licensed for the treatment of hypertriglyceridaemia considered a dose-dependent increased risk of atrial fibrillation which had been identified by several meta-analyses of large randomised controlled trials. These trials investigated the effect on cardiovascular outcomes compared with placebo enrolling more than 80,000 patients, mostly with cardiovascular diseases or cardiovascular risk factors. The frequency of atrial fibrillation was determined as "common" since, from this data, the incidence would be 3.9%.

The findings of this review were considered by the Pharmacovigilance Expert Advisory Committee (PEAG) of the Commission on Human Medicines, which agreed with the recommendations of European regulators to update the product information. A letter has been sent to United Kingdom healthcare professionals. The product information recommends permanent discontinuation of treatment for patients who develop atrial fibrillation whilst taking these medicines for hypertriglyceridaemia. Clinical judgment and assessment of the individual benefits and risks to the patient should be taken into consideration before any decision to stop treatment. The PEAG noted that, in the case of patients with a previous or current diagnosis of atrial fibrillation, the product information does not provide specific advice or contraindicate use of these medicines.

The MHRA does not regulate food or dietary supplements that are marketed without reference to a medicinal effect/claim. Neither the randomised controlled trials or the review evaluated dietary consumption of fish and other foods rich in omega-3 nor supplements, and the MHRA is unable to give advice on the risk in individuals who consume dietary omega-3 supplements without a known history of cardiovascular disease or significant cardiovascular risk factors.

Up to 13 November 2023, the MHRA has not received any Yellow Card reports describing atrial fibrillation in association with a medicinal product containing omega-3 acids as the active substance.

Advice for healthcare professionals:

- Atrial fibrillation is now listed as an adverse drug reaction with a "common" frequency (may affect up to 1 in 10 people) for medicines containing omega-3-acid ethyl esters licensed for the treatment of hypertriglyceridaemia.
- The observed risk was found to be highest with a dose of 4g/day.
- Advise patients taking omega-3-acid ethyl ester medicines for the treatment of hypertriglyceridaemia to seek medical attention if they develop symptoms of atrial fibrillation (include palpitations, dizziness, shortness of breath and tiredness).
- If a patient develops atrial fibrillation whilst taking these medicines for the treatment of hypertriglyceridaemia then the medicine should be discontinued permanently.

In Hong Kong, Omacor Capsules 1000mg (HK-66442) is a pharmaceutical product registered by Lee's Pharmaceutical (HK) Limited. It is a prescription-only medicine. Teromeg 1000mg capsules is not a registered pharmaceutical product. As of the end of January 2024, the Department of Health (DH) had not received any case of adverse drug reaction related to omega-3-acid ethyl esters. Related news was previously issued by European Medicines Agency, and was reported in Drug News Issue No. 167. The DH issued letters to inform local healthcare professionals to draw their attention on 3 October 2023. As previously reported, the matter will be discussed by the Registration Committee of the Pharmacy and Poisons Board .

**The United States: BCMA- and CD19-directed genetically modified autologous chimeric antigen receptor (CAR) T cell immunotherapies: risk of T cell malignancies**

On 23 January 2024, the US Food and Drug Administration (FDA) announced that the FDA issued safety labeling change notification letters to all manufacturers of licensed BCMA- and CD19-directed genetically modified autologous chimeric antigen receptor (CAR) T cell immunotherapies (Abecma, Breyanzi, Carvykti, Kymriah, Tecartus, Yescarta) requiring a revision to the package insert due to risk of T cell malignancies, with serious outcomes, including hospitalization and death.

The FDA considers the serious risk of T cell malignancy to be applicable to all BCMA- and CD19-directed genetically modified autologous T cell immunotherapies. The letters notify manufacturers of each such licensed product to update the package insert to include available

information related to the risks and to update the Medication Guide for these products to identify the possibility of the increased risk of getting cancers, including certain types of cancers of the immune system.

In November 2023, the FDA posted a safety communication to provide information related to the receipt of reports of T cell malignancies, including CAR-positive lymphoma, in patients who received treatment with BCMA- or CD19-directed autologous CAR T cell immunotherapies. Reports were received from clinical trials and/or postmarketing adverse event data sources. Although the overall benefits of these products continue to outweigh their potential risks for their approved uses, the FDA continues to investigate the identified risk of T cell malignancy with serious outcomes, including hospitalization and death.

Patients and clinical trial participants receiving treatment with these products should be monitored life-long for new malignancies. In the event that a new malignancy occurs following treatment with these products, clinicians are encouraged to contact the manufacturer to report the event and obtain instructions on collection of patient samples for testing for the presence of the CAR transgene.

In Hong Kong, Kymriah (tisagenlecleucel) Dispersion For Infusion (HK-66588) is a pharmaceutical product registered by Novartis Pharmaceuticals (HK) Limited. It is a prescription-only medicine. As of the end of January 2024, with regard to tisagenlecleucel, the Department of Health (DH) had received 18 cases of adverse drug reaction, of which 8 cases were reported as malignancies. The other products mentioned in the above FDA's announcement are not registered pharmaceutical products.

Related news was previously issued by FDA and European Medicines Agency, and was reported in Drug News Issue No. 169. In light of the above FDA's announcement, the DH issued letters to inform local healthcare professionals to draw their attention on 24 January 2024, and the matter will be discussed by the Registration Committee of the Pharmacy and Poisons Board.

**Taiwan: Safety-related information for medicines containing mifepristone**

On 23 January 2024, the Taiwan Food and Drug Administration (TFDA) announced a safety-related information for the product Mifegyne (mifepristone) that is released by Swissmedic. (Please refer to the website in Swissmedic for details: https://www.swissmedic.ch/swissmedic/en/home/humanarzneimittel/market-surveillance/health-professional-communication--hpc-/dhpc-mifegyne-mifepristonum.html)

Two cases of acute generalized exanthematous pustulosis (AGEP) have been reported in literature with close temporal relationship with mifepristone intake. AGEP is a rare, acute, severe cutaneous adverse reaction attributed mainly to drugs, although other triggers, including infections, vaccinations, ingestion of various substances, and spider bites, have also been reported. The mainstay of treatment for AGEP is withdrawal of the offending drug. In cases caused by infection or other triggers rather than a drug, treatment of the underlying cause is an important part of management. The reaction usually resolves within 15 days, and the overall prognosis is good.

The Swissmedic had adopted the decision by the European Health Authority on the inclusion of a warning in section "Warnings and precautionary measures" of the summary of product characteristics (SmPC), the addition of acute generalized exanthematous pustulosis (AGEP) in section "Adverse effects" and an update of sections "Possible side effects" and "What you need to know before taking Mifegyne?" of the package leaflet. The current Mifegyne Tablets 200mg and Mifegyne Tablets 600mg packages on the Swiss market do not contain the most recently approved Patient Information Leaflet. The new adverse event acute generalized exanthematous pustulosis (AGEP) is missing under section "Possible side effects" of the leaflet.

Please refer to the following website in TFDA for details: https://www.fda.gov.tw/TC/siteList.aspx?sid=1571

In Hong Kong, there are 2 registered pharmaceutical products containing mifepristone. These products are prescription-only medicines. As of the end of January 2024, the Department of Health (DH) had not received any case of adverse drug reaction related to mifepristone. In light of the above TFDA's announcement, the DH issued letters to inform local healthcare professionals to draw their attention on 24 January 2024 and 25 January 2024. The DH will remain vigilant on

safety update of the drug issued by other overseas drug regulatory authorities for consideration of any action deemed necessary.

**European Union: EMA confirms measures to minimise the risk of serious side effects with medicines containing pseudoephedrine**

On 26 January 2024, the European Medicines Agency (EMA) announced that its human medicines committee (CHMP) endorsed the measures recommended by the Pharmacovigilance Risk Assessment Committee (PRAC) to minimise the risks of posterior reversible encephalopathy syndrome (PRES) and reversible cerebral vasoconstriction syndrome (RCVS) for medicines containing pseudoephedrine.

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. CHMP confirmed that 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 in patients with severe acute (sudden) or chronic (long-term) kidney disease or failure.

In addition, 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 recommendations follow a review of all available evidence, including post-marketing safety data, which concluded that pseudoephedrine is associated with risks of PRES and RCVS. During the review, PRAC sought advice from an expert group of general practitioners, otorhinolaryngologists (specialists in diseases of the ear, nose, throat, head and neck), allergologists (specialists in the treatment of allergies) and a patient representative. PRAC also considered information submitted by a third party representing healthcare professionals.

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. Restrictions and warnings are already included in the product information of these medicines to reduce cardiovascular and cerebrovascular ischaemic (involving reduced blood supply to the heart and brain) risks.

The CHMP opinion will now be sent to the European Commission, which will issue a legally binding decision across the EU.

Information for healthcare professionals:

- An EMA review has found that pseudoephedrine-containing medicines are associated with risks of posterior reversible encephalopathy syndrome (PRES) and reversible cerebral vasoconstriction syndrome (RCVS), serious conditions affecting the cerebral blood vessels. This follows an evaluation of all available data including few reported cases of these conditions.
- There were no fatal cases of PRES or RCVS reported, and most of the cases resolved following discontinuation of the medicine and appropriate treatment.
- Pseudoephedrine-containing medicines must not be used in patients with severe or uncontrolled hypertension or severe acute or chronic kidney disease or renal failure, as these are risk factors for developing PRES or RCVS.
- Patients should be advised to discontinue treatment and seek immediate medical assistance if they develop symptoms of PRES or RCVS such as sudden, severe headache or thunderclap headache, nausea, vomiting, confusion, seizures and/or visual disturbances.
- The risks of PRES and RCVS should be considered alongside other risks associated with pseudoephedrine-containing medicines, including cardiovascular or ischaemic events.

A direct healthcare professional communication (DHPC) will be sent in due course to relevant healthcare professionals. The DHPC will also be published on a dedicated page on the EMA website.

In Hong Kong, there are 100 registered pharmaceutical products containing pseudoephedrine. All products are pharmacy only medicines. As of the end of January 2024, 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 and 170. The DH issued letters to inform local healthcare professionals to draw their attention on 4 December 2023. As previously reported, the matter will be discussed by the Registration Committee of the Pharmacy and Poisons Board.

**European Union: Precautionary measures to address potential risk of neurodevelopmental disorders in children born to men treated with valproate medicines**

On 26 January 2024, the European Medicines Agency (EMA) announced that the Coordination Group for Mutual Recognition and Decentralised Procedures (CMDh) endorsed precautionary measures recommended by EMA's safety committee (PRAC) for the treatment of male patients with valproate medicines. These measures are to address a potential increased risk of neurodevelopmental disorders in children born to men treated with valproate during the 3 months before conception. Valproate medicines are used to treat epilepsy, bipolar disorders and, in some EU countries, migraine.

It is recommended that valproate treatment in male patients is started and supervised by a specialist in the management of epilepsy, bipolar disorder or migraine.

Doctors should inform male patients who are taking valproate about the possible risk and discuss the need to consider effective contraception, for both the patient and their female partner. Valproate treatment of male patients should be reviewed regularly to consider whether it remains the most suitable treatment, particularly when the patient is planning to conceive a child.

In reaching its conclusion, the PRAC reviewed data from a retrospective observational study carried out by companies that market valproate as an obligation following a previous review of valproate use during pregnancy. The Committee also considered data from other sources, including non-clinical (laboratory) studies and scientific literature, and consulted patients and clinical experts.

The retrospective observational study used data from multiple registry databases in Denmark, Norway and Sweden and focused on birth outcomes in children born to men who were taking valproate or taking lamotrigine or levetiracetam (other medicines to treat conditions similar to those treated with valproate) around the time of conception.

The results of the study suggest there may be an increased risk of neurodevelopmental disorders in children born to men taking valproate in the 3 months before conception. Neurodevelopmental disorders are problems with development that begin in early childhood, such as autism spectrum disorders, intellectual disability, communication disorders, attention deficit/hyperactivity disorders and movement disorders.

The data showed that around 5 out of 100 children had a neurodevelopmental disorder when born to fathers treated with valproate compared with around 3 out of 100 when born to fathers treated with lamotrigine or levetiracetam. The study did not investigate the risk in children born to men who stopped using valproate more than 3 months before conception.

The possible risk in children born to men treated with valproate in the 3 months before conception is lower than the previously confirmed risk in children born to women treated with valproate during pregnancy. It is estimated that up to 30 to 40 out of 100 preschool children whose mothers took valproate during pregnancy may have problems with early childhood development, such as being slow to walk and talk, being intellectually less able than other children, and having difficulty with language and memory.

The study data on male patients had limitations, including differences between the groups in the conditions for which the medicines were used and in follow-up times. The PRAC could therefore not establish whether the increased occurrence of these disorders suggested by the study was due to valproate use. In addition, the study was not large enough to identify which types of neurodevelopmental disorders children could be at increased risk of developing. Nonetheless, the Committee considered precautionary measures were warranted to inform patients and healthcare professionals.

The potential risk of neurodevelopmental disorders and the precautionary measures will be reflected in updates to the product information and educational material for valproate medicines.

Following the adoption of the PRAC

recommendations by the CMDh, these measures will now be implemented in all Member States where valproate-containing medicines are authorised.

Information for healthcare professionals:

- It is recommended that valproate treatment in male patients is initiated and supervised by a specialist in the management of epilepsy, bipolar disorder or migraine.
- Healthcare professional should:
  - inform male patients currently being treated with valproate of the potential risk of neurodevelopmental disorders and consider whether valproate remains the most appropriate treatment;
  - discuss with male patients the need to consider effective contraception, including for their female partner, while using valproate and for at least 3 months after stopping treatment;
  - inform male patients about the need for regular reviews by their doctor to assess if valproate remains the most appropriate treatment for the patient and discuss suitable treatment alternatives with the patient. This is particularly important if the male patient is planning to conceive a child and, in this case, before discontinuing contraception;
  - advise male patients not to donate sperm during treatment and for at least 3 months after treatment discontinuation;
  - provide male patients with the new patient guide for male patients and alert them to the patient card attached to, or included in, their medicine's packaging.
- These precautionary measures are based on a PRAC review of data from a retrospective observational study (EUPAS34201). The results suggest an increased risk of neurodevelopmental disorders in children born to men treated with valproate in the 3 months prior to conception compared with the risk in those born to men treated with lamotrigine or levetiracetam.
- Meta-analysis of data from 3 Nordic countries resulted in a pooled adjusted hazard ratio (HR) of 1.50 (95% CI: 1.09-2.07) for neurodevelopmental disorders in children of fathers treated with valproate in the 3 months prior to conception compared with lamotrigine or levetiracetam. The adjusted cumulative risk of neurodevelopmental disorders was estimated to be around 5% in the valproate group versus around 3% in the lamotrigine and levetiracetam group. No difference in the risk of congenital malformations was seen between the two groups.
- The study did not evaluate the risk of neurodevelopmental disorders in children born to fathers who stopped using valproate more than 3 months before conception.
- Previous recommendations to avoid exposure to valproate medicines in women during pregnancy due to the risk of congenital malformations and neurodevelopmental disorders remain in place.

A direct healthcare professional communication (DHPC) will be sent in due course to healthcare professionals prescribing, dispensing or administering the medicine. The DHPC will also be published on a dedicated page on the EMA website.

In Hong Kong, there are 10 registered pharmaceutical products containing valproate. All products are prescription-only medicines. As of the end of January 2024, the Department of Health (DH) had received 15 cases of adverse drug reaction related to valproate, but these cases were not related to neurodevelopmental disorders in children after paternal exposure to valproate.

Related news was previously issued by Singapore's Health Science Authority (HSA), the United Kingdom Medicines and Healthcare products Regulatory Agency (MHRA) and European Medicines Agency (EMA), and reported in the Drug News since Issue No. 161, with the latest update reported in Drug News Issue No. 166. The DH issued letters to inform local healthcare professionals to draw their attention on 22 March 2023. As previously reported, the matter will be discussed by the Registration Committee of the Pharmacy and Poisons Board.

# Drug Recall

**Batch recall of six products of Meyer Pharmaceuticals Ltd**

On 26 January 2024, the Department of Health (DH) had instructed a licensed drug manufacturer, Meyer Pharmaceuticals Ltd (Meyer), to recall the following six products from the market as a precautionary measure due to a quality issue.

| Name of product | Hong Kong registration number | Batch number/ Pack size | Main use |
|---|---|---|---|
| Lyhexine Cap | HK-37207 | 082208/10's | relief of cold and cough symptoms |
| Mecotuss Cap | HK-35597 | 052104-3/1000's<br>052105-3/1000's<br>052104-2/24's<br>052105-2/24's<br>052104-1/12's<br>052105-1/12's<br>052106-1/12's | relief of cold and cough symptoms |
| Betamin Tab* | HK-32501 | 102206-1/100s<br>102206-2/1000s | relief of allergy symptoms |
| Sensoderm-S Cream* | HK-36365 | 012203/18g<br>112109-3/450g | treating skin infections |
| Xanaderm Cream* | HK-41063 | 112108/20g | treating skin infections |
| Mobeta Cream* | HK-37738 | 012207/20g | treating skin infections |

*Prescription drugs

Upon receiving a public complaint, the DH has conducted an investigation against Meyer. The investigation revealed that the content of the active ingredients in the products failed to meet the product specifications during a long-term stability study.

While the problem identified will affect the stability of the products, it would not be harmful to user. As a precautionary measure, the DH has instructed Meyer to recall the products from the market. The DH's investigation is continuing.

According to Meyer, the products have been supplied to local private doctors, pharmacies and medicine companies. As of the end of January 2024, the DH had not received any adverse reaction reports in connection with the above products. A press release was posted in the Drug Office website on 26 January 2024 to alert the public of the product recall. The DH will closely monitor the recall.

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/**

## *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,***
***Room 1856, 18/F, Wu Chung House,***
***213 Queen's Road East,***
***Wanchai, 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.***