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Safety Update

European Union: PRAC recommends new measures to avoid topiramate exposure in pregnancy

On 1 September 2023, the European Medicines Agency (EMA) announced that its safety committee, the Pharmacovigilance Risk Assessment Committee (PRAC), recommends new measures to avoid exposure of children to topiramate-containing medicines in the womb, because the medicine may increase the risk of neurodevelopmental problems after exposure during pregnancy. Topiramate is already known to cause serious birth defects when used during pregnancy.

Topiramate-containing medicines are used in the European Union for the treatment of epilepsy and prevention of migraine. In some European Union countries, the medicine is also used in combination with phentermine for weight reduction. At present, topiramate must not be used to prevent migraine or manage body weight during pregnancy and patients who can become pregnant must use effective birth control when using topiramate.

For patients using topiramate for the treatment of epilepsy, the PRAC is now recommending that the medicine should not be used during pregnancy unless there is no other suitable treatment available. The PRAC also recommends additional measures, in the form of a pregnancy prevention programme, to avoid exposure of children to topiramate in the womb. These measures will inform any woman or girl who is able to have children of the risks of taking topiramate during pregnancy and the need to avoid becoming pregnant while taking topiramate.

Healthcare professionals should ensure that all patients who can become pregnant are fully aware of the risks of taking topiramate during pregnancy. Alternative treatment options should be considered and the need for topiramate treatment should be reassessed at least annually. The product information for topiramate-containing medicines will be updated to further highlight the risks and the measures to be taken. Patients and healthcare professionals will be provided with educational materials regarding the risks of using topiramate during pregnancy, and a patient card will be provided to the patient with each medicine package. A visible warning will also be added to the outer packaging of the medicine.

The recommendations follow the PRAC's review of available data, including three recent observational studies. Two of these studies, which used largely the same datasets, suggest that children born to mothers with epilepsy and who were exposed to topiramate in the womb may have a two- to three-fold higher risk of neurodevelopmental disorders, in particular autism spectrum disorders, intellectual disability or attention deficit hyperactivity disorder (ADHD), compared with children born to mothers with epilepsy not taking antiepileptic medication. The third study did not show an increased risk of these outcomes in children born to mothers exposed to topiramate in pregnancy, compared with children born to women with epilepsy not taking antiepileptic medication.

In its review, the PRAC confirmed the known increased risk of birth defects and reduced growth of the unborn child when mothers receive topiramate during pregnancy. Birth defects will occur in 4 to 9 out of every 100 children born to women who take topiramate during pregnancy, compared with 1 to 3 out of every 100 children born to women who do not take such treatment. Further, around 18 in every 100 children were smaller and weighed less than expected at birth when mothers had taken topiramate during pregnancy, compared

with 5 in every 100 children born to mothers without epilepsy and not taking antiepileptic medication.

The companies that market topiramate must carry out a drug utilisation study and surveys of healthcare professionals and patients to assess the effectiveness of the new measures.

The PRAC recommendations will now be sent to the Co-ordination Group for Mutual Recognition and Decentralised Procedures – Human (CMDh), which will adopt a position.

Information for healthcare professionals:

- It is already well known that topiramate can cause major congenital malformations and foetal growth restriction when used during pregnancy. Recent data also suggest a possibly increased risk of neurodevelopmental disorders following topiramate use during pregnancy.
- In the prevention of migraine and as treatment for weight management, topiramate is contraindicated during pregnancy. Topiramate must be discontinued if the patient becomes pregnant or is planning for a baby. Patients of childbearing potential should use highly effective contraception during treatment and for at least 4 weeks after stopping topiramate treatment.
- In the treatment of epilepsy, topiramate is contraindicated during pregnancy unless there is no suitable treatment alternative. Topiramate is also contraindicated in women of childbearing potential with epilepsy not using highly effective contraception. The only exception is a woman for whom there is no suitable alternative but who is planning a pregnancy and who has been fully informed about the risks of taking topiramate during pregnancy.
- Irrespective of indication, topiramate should be used in women of childbearing potential only when the following conditions of the pregnancy prevention programme are met: a pregnancy test before starting treatment; counselling about the risks of topiramate treatment and the need for highly effective contraception throughout treatment; a review of ongoing treatment at least annually by completion of a risk awareness form.
- To confirm that appropriate measures have been taken, patients and prescribers will go through this form at the beginning of treatment and at each annual review and if the patient is planning a pregnancy or has become pregnant. It should be ensured that the patient is fully informed and has understood the risks and measures to be taken.
- Topiramate treatment of patients of childbearing potential should be initiated and supervised by a physician experienced in the management of epilepsy or migraine. Treatment with topiramate/phentermine should be handled by a physician experienced in weight management. Alternative therapeutic options should be considered and the need for treatment should be reassessed together with the patient at least annually. Ongoing treatment should be re-evaluated to confirm that the measures outlined above have been taken.

In Hong Kong, there are 26 registered pharmaceutical products containing topiramate. All products are prescription-only medicines. As of the end of September 2023, the Department of Health (DH) had received 5 cases of adverse drug reaction related to topiramate, but these cases were not related to neurodevelopmental disorders in children exposed to topiramate in utero.

Currently, the package insert and/or sales pack label of locally registered topiramate-containing products should include safety information on fetal harm and the increased risk of cleft lip and/or cleft palate (oral clefts) in infants exposed to topiramate in utero.

Related news on the risk of neurodevelopmental disorders in children exposed to topiramate in utero was previously issued by various overseas drug regulatory authorities, and was reported in the Drug News since Issue No. 153, with the latest update reported in Drug News Issue No. 161.

In light of the above EMA's announcement, the DH issued letters to inform local healthcare professionals to draw their attention on 4 September 2023, and the matter will be discussed by the Registration Committee of the Pharmacy and Poisons Board.

Taiwan: Safety information for Dipeptidyl Peptidase 4 (DPP-4) Inhibitors

On 6 September 2023, the Taiwan Food and Drug Administration (TFDA) announced that the Taiwan National Adverse Drug Reaction (ADR) Reporting

Center has received several reports of serious ADR cases on bullous pemphigoid, including death cases, which is suspected to be associated with the use of Dipeptidyl Peptidase 4 (DPP-4) inhibitors.

Considering that there is literature supporting the risk of developing bullous pemphigoid associated with the use of DPP-4 inhibitors and the serious ADR cases of bullous pemphigoid (including death cases) that have been reported with DPP-4 inhibitors use in Taiwan, the Taiwan Food and Drug Administration (TFDA) issued an alert to remind healthcare professionals and public to be aware of the relevant risks associated with the use of DPP-4 Inhibitors in order to ensure public safety on medication use.

Healthcare professionals should take note of the followings:

- Serious ADR cases of bullous pemphigoid have been reported with DPP-4 inhibitor use. In reported cases, patients typically responded to topical or systemic immunosuppressive treatment and discontinuation of the DPP-4 inhibitor, but there are still death cases reported.
- When prescribing a DPP-4 inhibitor, if a patient develops blisters or erosions (skin or oral/mucosal), or bullous pemphigoid is suspected while receiving a DPP-4 inhibitor, this medicinal product should be discontinued and patients should be referred to a dermatologist for diagnosis and appropriate treatment.

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 registered pharmaceutical products containing alogliptin (7 products), linagliptin (6 products), saxagliptin (5 products), sitagliptin (12 products) and vildagliptin (12 products). All products are prescription-only medicines. As of the end of September 2023, the Department of Health (DH) had received cases of adverse drug reactions related to alogliptin (1 case), linagliptin (4 cases), sitagliptin (9 cases) and vildagliptin (2 cases), but these cases are not related to bullous pemphigoid. The DH had not received any cases of adverse drug reactions related to saxagliptin. Relevant safety information on bullous pemphigoid associated with the use of DPP-4 inhibitors is documented in reputable references, such as the American Hospital Formulary Service Drug Information (AHFS).

In light of the above TFDA's announcement, the DH issued letters to inform local healthcare professionals to draw their attention on 7 September 2023. The DH will remain vigilant on any safety update of the drug issued by other overseas drug regulatory authorities for consideration of any action deemed necessary.

European Union: EMA recommends non-renewal of authorisation of multiple myeloma medicine Blenrep

On 15 September 2023, the European Medicines Agency (EMA) announced that its human medicines committee (CHMP) has recommended not renewing the conditional marketing authorisation for Blenrep (belantamab mafodotin), a medicine used to treat multiple myeloma (a cancer of the bone marrow). Blenrep is given to adults who have received at least four previous treatments and whose disease does not respond to certain other types of cancer treatment, and whose cancer has worsened since receiving the last treatment.

This recommendation follows a review of available data by the CHMP as part of the renewal of Blenrep's marketing authorisation. In its review, the CHMP considered that results from a new study (DREAMM-3) did not confirm the effectiveness of Blenrep as agreed when conditional marketing authorisation was granted.

Because Blenrep was meant to address an unmet medical need for a serious disease, it received a conditional marketing authorisation in August 2020. This type of authorisation allows a medicine to be authorised on the basis of less comprehensive (complete) data than are normally required, and when the benefits of having the medicine available earlier outweigh any risks associated with using it while waiting for further evidence. Medicines with a conditional marketing authorisation are subject to specific post-authorisation obligations (such as a new study) that aim to generate comprehensive data on these medicines.

At the time of the initial authorisation, no comparative data for Blenrep were available. As a specific obligation, the CHMP therefore requested the company marketing Blenrep to carry out a study to confirm the safety and effectiveness of the medicine by comparing it with pomalidomide plus

low-dose dexamethasone, another authorised treatment for multiple myeloma that has come back and has not responded to treatment.

The study found that patients who received Blenrep did not live longer without their disease getting worse than those who received pomalidomide plus dexamethasone. As this was the measure of effectiveness requested as part of the specific obligation, the medicine's effectiveness could not be confirmed in its authorised use. Therefore, the CHMP recommended not renewing the marketing authorisation in the EU.

In its review the CHMP also consulted patient representatives and experts in the treatment of cancer and took their views into consideration when reaching its opinion.
EMA will now send the CHMP's opinion to the European Commission, which will issue a final legally binding decision applicable in all EU Member States.

Information for patients:

- The marketing authorisation for Blenrep will not be renewed and the medicine will no longer be available in the EU.
- Blenrep was approved to treat a serious disease called 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 study failed to show that patients treated with Blenrep lived longer without their disease getting worse than those treated with pomalidomide and low-dose dexamethasone, another authorised treatment for multiple myeloma.
- As this was the measure of effectiveness requested at the time the medicine was granted conditional authorisation, the medicine's effectiveness could not be confirmed in its authorised use.
- If you are receiving Blenrep, you should speak to your doctor about possible treatment alternatives.

Information for healthcare professionals:

- Blenrep will no longer be available following non-renewal of its conditional marketing authorisation.
- Healthcare professionals should not start any new patients on Blenrep.
- For patients currently using Blenrep, healthcare professionals should explain to patients that the medicine is no longer available and discuss with them suitable treatment alternatives.
- 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 their disease getting worse 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. As of the end of September 2023, the Department of Health (DH) had received 5 cases of adverse drug reaction. In light of the above EMA's announcement, the DH issued letters to inform local healthcare professionals to draw their attention on 18 September 2023, and the matter will be discussed by the Registration Committee of the Pharmacy and Poisons Board .

Singapore: Reminder on the risk of pholcodine-associated perioperative anaphylaxis with neuromuscular blocking agents

On 21 September 2023, the Health Sciences Authority (HSA) announced that all pholcodine-containing medicines have been withdrawn in Singapore with effect from 22 June 2023. HSA had, in consultation with its Product Vigilance Advisory Committee, concluded that the benefit of pholcodine for the symptomatic relief of non-productive cough did not outweigh the potential increased risk of perioperative

anaphylaxis (POA) with neuromuscular blocking agents (NMBAs). The product registrant had cancelled the registrations for all pholcodine-containing products in Singapore and ceased their supply to pharmacies, clinics and healthcare institutions in June 2023.

Since data from a post-authorisation study showed that the use of pholcodine during the 12 months preceding anaesthesia was associated with an increased risk of POA with NMBAs, the risk period is considered relatively long. Therefore, anaesthesiologists and anaesthetists are advised to ask patients who are scheduled to undergo general anaesthesia with NMBAs, whether they have used pholcodine, particularly in the past 12 months, and to maintain clinical vigilance for potential NMBA-related POA in their patients.

The Allergy to Neuromuscular Blocking Agents and Pholcodine Exposure (ALPHO) study was a post-authorisation safety study imposed by the European Medicines Agency (EMA) on pholcodine -containing products to investigate the possibility of an association between pholcodine use and NMBA-related anaphylaxis. It was a multicentre case-control study comparing pholcodine exposure within a year before anaesthesia between patients with NMBA-related POA (cases) and control patients with uneventful anaesthesia. Each case was matched to two controls by age, sex, type of NMBA, geographic area and anaesthesia period. A total of 167 NMBA-related POA cases were matched with 334 control patients. Overall, 47% of cases and 20% of controls reported the use of pholcodine in the year preceding the anaesthesia index ($p<0.001$). The multivariable analysis showed that pholcodine consumption was associated with NMBA-related POA with an adjusted odds ratio of 4.2 (95% confidence interval 2.3-7.0).

Pholcodine is suspected to cross-sensitise individuals to NMBAs by inducing the production of immunoglobulin E (IgE) antibodies, thereby increasing their susceptibility to develop POA to NMBAs. Although the underlying pathogenic mechanisms have yet to be elucidated, the IgE binding epitopes on both pholcodine and NMBAs contain quaternary ammonium. The ALPHO study found the positive predictive value for specific IgE antibodies to pholcodine and quaternary ammonium to be very low (up to only 5.3%), suggesting that only a small proportion of patients (~ 5 out of 100) who have IgE antibodies to pholcodine/quaternary ammonium will develop POA to NMBAs. This precludes the use of these biomarkers to identify pholcodine-exposed patients who are at high risk of developing POA to NMBAs.

Several regulatory agencies, including the EMA, Australia Therapeutic Goods Administration, United Kingdom Medicines and Healthcare Products Regulatory Agency, Malaysia National Pharmaceutical Regulatory Agency and Hong Kong Department of Health, have announced the withdrawal of pholcodine-containing products in their jurisdictions. These actions were taken following their review of the ALPHO study results and other available information.

HSA's assessment took into consideration the findings from the ALPHO study, use of pholcodine in the local context, availability of therapeutic alternatives, expert opinions of local healthcare professionals and the regulatory actions taken by the international health regulatory authorities.

POA is a potentially life-threatening systemic hypersensitivity reaction that typically manifests abruptly after induction of anaesthesia, with severe symptoms that require immediate diagnosis and treatment. The local incidence of POA is considered to be rare and ranges from 1 to 4 in 10,000, with NMBAs identified as the causative agent for up to half of these cases. The clinical presentation of POA can vary across patients depending on the triggering agent, underlying comorbidities and concomitant use of other drugs. Hence, the outcome of any NMBA-related POA is dependent on the timeliness and effectiveness of the recognition and management of the anaphylaxis.

The overall absolute risk of pholcodine-associated POA with NMBAs was assessed to be very small given the rare NMBA-specific incidence of POA reported locally and that the risk applies to a small subset of patients with prior exposure to pholcodine who are subjected to an NMBA during the perioperative period. However, there are no effective risk mitigation measures that can reduce the risk of pholcodine-associated POA with NMBAs in individual patients. There are no biomarkers or tests that can predict which pholcodine-exposed patients will develop POA to NMBAs, and it may not be possible to accurately obtain history of pholcodine use due to poor patient recollection or in situations of emergency surgeries.

There is also uncertainty of a longer risk period beyond 12 months.

To date, HSA has not received any local reports of POA to NMBAs associated with prior pholcodine use, although the possibility of under reporting of cases cannot be ruled out.

Considering the serious and life-threatening nature of POA, the clinical necessity of using NMBAs during anaesthesia, the non-serious and self-limiting nature of non-productive coughs, as well as the availability of therapeutic alternatives, HSA concluded that the benefit of pholcodine did not outweigh its associated risk of cross-sensitisation and POA to NMBAs.

In Hong Kong, there are 27 registered pharmaceutical products containing pholcodine. All products are pharmacy-only medicines. As of the end of September 2023, the Department of Health (DH) had received one case of adverse drug reaction related to pholcodine, but this case was not related to anaphylaxis. Related news was previously issued by various overseas drug regulatory authorities, and was reported in the Drug News since Issue No. 17, with the latest update reported in Drug News Issue No. 164. The DH issued letters to inform local healthcare professionals to draw their attention on 1 March 2023.

In April 2023 and July 2023, the Registration Committee of the Pharmacy and Poisons Board discussed the matter, and decided to de-register pharmaceutical products containing pholcodine with effect from 1 January 2024 because the benefits of the products no longer outweigh their risks. A press statement was issued on 7 July 2023. The DH issued letters to healthcare professionals and pharmaceutical traders to inform them of the Committee's decision, and to advise healthcare professionals to arrange suitable alternative treatments for their patients on the same date.

Singapore: HSA is assessing the potential risk of suicidal thoughts and self-harm with glucagon-like peptide-1 receptor agonists (GLP-1 RA)

On 21 September 2023, the Health Sciences Authority (HSA) announced that a safety review on the potential risk of suicidal thoughts and self-harm with glucagon-like peptide-1 receptor agonists (GLP-1 RA) was recently initiated by some overseas regulatory authorities due to emerging reports associated with the use of liraglutide and semaglutide for weight management. HSA is monitoring the international developments closely and working with the local product registrants to assess this potential safety concern. HSA will provide updates when its safety assessment is completed.

GLP-1 RA bind to the GLP-1 receptor and physiologically regulate appetite and calorie intake, thereby enhancing insulin secretion and slowing gastric emptying. They are indicated either for weight management or Type 2 diabetes mellitus (T2DM).

In July 2023, the European Medicines Agency (EMA) initiated its review on the potential risk of suicidal thoughts and self-harm in patients taking Saxenda (liraglutide), Wegovy (semaglutide) and Ozempic (semaglutide), due to reports flagged by the Icelandic medicines agency. Saxenda and Wegovy are authorised in the European Union for weight management, whereas Ozempic is indicated for T2DM but has been used off-label for weight loss. The analysis of the reports is ongoing, and it has not been confirmed whether these reports are linked to the drugs, the patients' underlying conditions or other factors. As further investigation of this signal was warranted, the EMA subsequently extended its review to include the entire class of GLP-1 RA. The United Kingdom Medicines and Healthcare Products Regulatory Agency has also initiated its review on GLP-1 RA due to domestic reports received on suicidal and self-injurious behaviour with the use of liraglutide and semaglutide.

There are currently eight GLP-1 RA products registered locally in Singapore: Saxenda (liraglutide), Wegovy (semaglutide), Trulicity (dulaglutide), Victoza (liraglutide), Soliqua (lixisenatide with insulin glargine), Rybelsus (semaglutide), Ozempic (semaglutide) and Mounjaro (tirzepatide). To date, HSA has not received any local adverse event (AE) reports of suicidal thoughts or self-harm associated with GLP -1 RA. Healthcare professionals are advised to exercise caution in the use of GLP-1 RA and report suspected serious AEs related to these products to the Vigilance and Compliance Branch of HSA.

In Hong Kong, there are registered pharmaceutical products containing dulaglutide (4 products), exenatide (1 product), liraglutide (3 products),

lixisenatide (2 products) and semaglutide (6 products). All products are prescription-only medicines. There is no registered pharmaceutical product containing tirzepatide. As of the end of September 2023, 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 (3 cases), but these cases were not related to suicidal thoughts or self-injury. Related news was previously issued by European Medicines Agency, and was reported in Drug News Issue No. 165. 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.

Singapore: Biotin interference with thyroid function tests

On 21 September 2023, the Health Sciences Authority (HSA) announced that biotin may interfere with thyroid function tests.

Biotin, also known as vitamin B7, is involved in the metabolism of fats, carbohydrates and amino acids required in protein synthesis. It is commonly present in health supplements (such as multivitamins, prenatal vitamins, and products promoting hair, skin and nail growth), and may interfere with thyroid function tests that are based on a biotin/streptavidin interaction. Depending on the assay design, this may lead to either falsely decreased or falsely increased test results, resulting in potential patient mismanagement or misdiagnosis. The risk of interference increases with higher doses of biotin. Healthcare professionals are reminded to consider the possibility of biotin interference when interpreting results of thyroid immunoassays, especially when the results do not match the clinical presentation.

Thyroid function tests measure the levels of thyroid hormones in the blood including thyroxine (T4) and triiodothyronine (T3), as well as thyroid stimulating hormone (TSH). These tests are critical in diagnosing and monitoring thyroid disorders, such as hyperthyroidism and hypothyroidism. Generally, there are two types of thyroid immunoassays used in the measurement of thyroid function. They are the sandwich assay to measure larger molecules such as TSH, and the competitive assay to measure small molecules such as T3 and T4. These immunoassays utilise the interaction between biotin and streptavidin (a glycoprotein) as a detection method due to the specific binding between the two biomolecules. Exogenous biotin (e.g., from multivitamins or supplements for hair, skin and nails) can therefore interfere with both types of immunoassays, resulting in either a falsely decreased or falsely increased test result, depending on the assay design. This potential interaction has been reported with oral products containing ≥ 150 mcg biotin per dose unit and parenteral products containing ≥ 60 mcg biotin per dose unit.

In a TSH sandwich assay, excess biotin occupies the streptavidin binding sites and prevents the binding of TSH-antibody sandwich complex, causing falsely low assay results. Conversely, in competitive immunoassays where the endogenous analyte (i.e., T3 or T4) competes with the labelled analyte (i.e., source of the signal) for biotinylated antibody binding sites, excess biotin levels result in falsely high assay results. This is because biotin prevents the binding of antibody-labelled analyte and antibody-endogenous analyte to the streptavidin-coated solid phase. The unbound antibodies are removed in the wash step, thereby removing any signal that indicates the concentration of endogenous analyte present. Since the serum concentration of the endogenous analyte is inversely proportional to the signal intensity, this results in falsely elevated values.

The interference of biotin with thyroid immunoassays is a known phenomenon and has been documented in several case reports. This had resulted in misdiagnosis or clinical mismanagement of thyroid disorders due to the dependence on thyroid function test results for the initiation or adjustment of thyroid medications.

In November 2022, the European Medicines Agency's Pharmacovigilance Risk Assessment Committee recommended for the addition of new warnings relating to biotin interference with thyroid function tests to the product information of levothyroxine-containing products. This followed their review on the possible biotin interference with thyroid function tests, which considered the information from spontaneous reports and literature.

In 2019, HSA had assessed the possibility of biotin interference with clinical laboratory tests, including thyroid function tests, and worked with the companies to include warnings on the possible interference in the local package inserts (PIs) of parenteral biotin-containing products. In view that

this safety concern may also affect patients who are on levothyroxine therapy, HSA has worked with the product registrants to include similar warnings on the possibility of biotin interference with thyroid function tests in the local PIs of levothyroxine products. To date, HSA has not received any local adverse event reports of biotin interference causing incorrect thyroid function test results.

Healthcare professionals are reminded to consider the possibility of biotin interference when interpreting results of thyroid function tests, especially if there is a lack of coherence with the clinical presentation observed. This may involve asking their patients about the use of biotin health supplements, such as those marketed for hair, skin and nail growth.

In Hong Kong, there are 8 registered pharmaceutical products containing biotin. Three of these products are oral preparations, and they are over-the-counter medicines. The other 5 products are injectables, and they are prescription-only medicines. There are 12 registered pharmaceutical products containing levothyroxine. All products are prescription-only medicines. As of the end of September 2023, the Department of Health (DH) had not received any case of adverse drug reaction related to biotin. The DH had received 5 cases of adverse drug reaction related to levothyroxine, but these cases were not related to biotin interference with laboratory tests.

Related news on biotin interference with laboratory tests which use biotin technology was previously issued by the United States Food and Drug Administration and HSA, and was reported in the Drug News since Issue No. 97, with the latest update reported in Drug News Issue No. 119. The DH issued letters to inform local healthcare professionals to draw their attention on 29 November 2017 and 7 November 2019 respectively. The DH will remain vigilant on any safety update of the drugs issued by other overseas drug regulatory authorities.

The United Kingdom: Fluoroquinolone antibiotics: suicidal thoughts and behavior

On 26 September 2023, the Medicines and Healthcare products Regulatory Agency (MHRA) announced that healthcare professionals prescribing fluoroquinolone antibiotics (ciprofloxacin, delafloxacin, levofloxacin, moxifloxacin, ofloxacin) are reminded to be alert to the risk of psychiatric reactions, including depression and psychotic reactions, which may potentially lead to thoughts of suicide or suicide attempts. Healthcare professionals are also reminded to advise patients to be alert to these risks.

The MHRA has received a Coroner's report following the death of a patient who died by suicide after being treated with ciprofloxacin. The patient had no previous history of depression or mental health problems. The Coroner raised concerns about the potential risk of suicidal behaviour in patients taking ciprofloxacin, the potential for increased risk in patients with depression, and the need to highlight this to healthcare professionals.

Warnings on the potential for psychiatric adverse drug reactions to occur with ciprofloxacin and other fluoroquinolones are included in the product information. The Summary of Product Characteristics states that psychiatric reactions may occur with ciprofloxacin, including after the first dose. In rare cases, depression or psychosis can progress to suicidal ideation or suicide attempts. If this happens, ciprofloxacin should be discontinued immediately. The Patient Information Leaflet advises patients that they may experience psychiatric reactions. If patients suffer from depression or psychosis before being prescribed this medication, their symptoms may become worse under treatment with ciprofloxacin. In rare cases, depression or psychosis can progress to thoughts of suicide or suicide attempts. If this happens, patients are advised to contact their doctor immediately.

It is not possible from available data to indicate a frequency nor period of risk for these potential adverse reactions. Patients should be advised to seek medical attention for any psychiatric symptoms, even if it has been some time since they stopped taking the medication.

Advice for healthcare professionals:

- Advise patients to carefully read the advice in the Patient Information Leaflet about possible psychiatric reactions, and to seek medical advice if they experience these symptoms.
- When prescribing a fluoroquinolone, advise patients to be alert to any mood changes, distressing thoughts, or feelings about suicide or harming themselves at any point during treatment.
- Note that fluoroquinolones can exacerbate

existing psychiatric symptoms.
- Advise patients to seek medical advice if they develop such thoughts or behaviours, and ensure that a suitable referral for treatment is made, if necessary.
- Fluoroquinolones should be discontinued at the first signs of a serious adverse reaction, including new or worsening depression or psychosis.

In Hong Kong, there are registered pharmaceutical products containing systemic fluoroquinolones for use in human, including ciprofloxacin (51 products), levofloxacin (45 products), moxifloxacin (6 products), norfloxacin (3 products), ofloxacin (15 products) and prulifloxacin (one product). All products are prescription-only medicines. There is no registered pharmaceutical product containing delafloxacin.

As of the end of September 2023, the Department of Health (DH) had received 4 cases of adverse drug reaction related to ofloxacin, all of these cases were related to attempted suicide/completed suicide. The DH had received adverse drug reaction related to ciprofloxacin (one case), levofloxacin (13 cases) and moxifloxacin (one case), but these cases were not related to depression, psychotic reactions, suicidal ideation or suicide. The DH had not received any case of adverse drug reaction related to norfloxacin and prulifloxacin.

The risk of depression, psychotic reactions, suicidal ideation and suicide associated with the use of fluoroquinolones is documented in overseas reputable drug references such as the "Martindale: The Complete Drug Reference". The DH will remain vigilant on any safety update of the drugs issued by other overseas drug regulatory authorities.

The United Kingdom: Statins: very infrequent reports of myasthenia gravis

On 26 September 2023, the Medicines and Healthcare products Regulatory Agency (MHRA) announced that there has been a very small number of reports of new onset or aggravation of pre-existing myasthenia gravis with atorvastatin, pravastatin, lovastatin, fluvastatin, simvastatin, rosuvastatin and pitavastatin (single-ingredient and fixed-dose combination products) globally.

A recent European review recommended new warnings on the risk of new onset or aggravation of pre-existing myasthenia gravis with multiple statins. 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. The product information of all statins is being updated to list myasthenia gravis and ocular myasthenia gravis as adverse drug reactions with a frequency 'not known'. New warnings will also be added to the Summaries of Product Characteristics and Patient Information Leaflets. In reviewing this issue, the PEAG recommended that the MHRA inform healthcare professionals and patients of the newly identified risk. They also noted that existing International Consensus Guidance for Management of Myasthenia Gravis (2020) states that statins may rarely worsen or precipitate myasthenia gravis.

Myasthenia gravis is a rare long-term auto-immune neuromuscular disorder characterised by fluctuating weakness of the voluntary muscles that control eye movements, facial expression, speaking, swallowing, limb movement and breathing. Symptoms include drooping eyelids, double vision, problems with chewing or swallowing, speech disturbance, limb weakness and shortness of breath. Myasthenia gravis can affect people of any age, generally starting in women under 40 years old and men over 60 years old. Drug treatment can usually help keep the symptoms under control. Several triggers have been identified for patients with myasthenia gravis that can aggravate symptoms. These include stress, tiredness, infections, excess physical activity, surgery, changes in immunomodulatory treatments and medicines. Some examples of medicines that have been associated with worsening symptoms include several groups of antibiotics and beta-blockers. Reports of worsening myasthenia gravis with medicines are very rare.

From 14 June 1995 up to 19 June 2023, the MHRA has received 10 United Kingdom Yellow Card reports citing a statin as a suspect medicine for an adverse drug reaction involving myasthenia gravis; with reports received for simvastatin, atorvastatin and pravastatin. This is against a background of extensive use of statins. In 2022 alone, more than 9.5 million patients were dispensed a statin in the United Kingdom. Across the 10 Yellow Card reports the median age of the patients was 66 years (affected patient age groups ranged from 40 to 89 years with the majority of reports concerning those aged over 60 years). Symptoms reported include

double vision, difficulty with speech and swallowing, weakness in limbs and shortness of breath. Onset of symptoms started from a few days up to three months after starting statin therapy. Three of the 10 cases involved the recurrence or exacerbation of symptoms in patients with known myasthenia gravis. There was also one report of positive rechallenge with symptoms recurring on reinitiating statin therapy. While four of the reports indicated that patients were hospitalised, the majority of patients had recovered or were recovering at the time of reporting. No fatal United Kingdom reports have been received.

At this time there is insufficient data to conclude whether different statins, different duration of therapy and different dosing levels alter the risk of experiencing myasthenia gravis. It is also unknown whether the development of new onset myasthenia gravis following statin therapy is a transient or permanent condition.

Advice for healthcare professionals:

- There have been some suspected reports of new onset or aggravation of pre-existing myasthenia gravis or ocular myasthenia gravis associated with statin use; the current frequency of these adverse events is not known but given the extensive use of statins in the population, the reports are understood to be very infrequent.
- The majority of United Kingdom reports note that the patient recovered after stopping statin treatment, while a minority continued to experience symptoms; recurrence of symptoms has been reported when patients restarted on the same or a different statin.
- Refer patients presenting with suspected new onset myasthenia gravis after starting statin therapy to a neurology specialist; it could be necessary to discontinue statin treatment depending on the assessment of the individual benefits and risks.
- Advise patients with pre-existing myasthenia gravis to be alert to aggravation of symptoms while taking a statin; it could be necessary to discontinue statin treatment depending on the assessment of the individual benefits and risks.

In Hong Kong, there are registered pharmaceutical products containing atorvastatin (104 products), lovastatin (3 products), pravastatin (8 products), rosuvastatin (67 products) and simvastatin (86 products). All products are prescription-only medicines. There is no registered pharmaceutical product containing fluvastatin or pitavastatin.

As of the end of September 2023, the Department of Health (DH) had received adverse drug reaction related to atorvastatin (21 cases), rosuvastatin (20 cases) and simvastatin (8 cases), but these cases were not related to myasthenia gravis. The DH had not received any case of adverse drug reaction related to lovastatin and pravastatin.

In light of the above MHRA's announcement, the DH issued letters to inform local healthcare professionals to draw their attention on 27 September 2023, and the matter will be discussed by the Registration Committee of the Pharmacy and Poisons Board.

European Union: New safety information for Omega-3-acid ethyl esters

On 29 September 2023, the European Medicines Agency (EMA) announced that the Pharmacovigilance Risk Assessment Committee (PRAC) agreed to add atrial fibrillation (irregular, rapid contraction of the heart) as a common side effect to the product information for medicines containing omega-3-acid ethyl esters. These medicines are indicated for the treatment of hypertriglyceridaemia, when a modification of diet and lifestyle alone are not sufficient to bring down levels of triglyceride, a type of fat, in the blood. Hypertriglyceridemia is a risk factor for coronary artery disease. Patients on these medications often have other conditions such as cardiovascular diseases and diabetes.

During a Periodic Safety Update Single Assessment procedure, the PRAC considered systematic reviews and meta-analyses of randomised controlled clinical trials which 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 esters compared to placebo. The observed risk is highest with a dose of 4 g daily. If atrial fibrillation develops, treatment should be permanently discontinued.

The PRAC agreed to recommend an update to the product information to inform healthcare professionals and patients of the risk of atrial fibrillation. A Direct Healthcare Professional Communication (DHPC) will be sent shortly to provide doctors with further details. Once adopted,

this DHPC will be forwarded to the Coordination Group for Mutual Recognition and Decentralised Procedures – Human (CMDh). Following the CMDh opinion, the DHPC will be disseminated to healthcare professionals by the marketing authorisation holder, according to an agreed communication plan, and published on the DHPCs page and in national registers in European Union Member States.

In Hong Kong, there is one registered pharmaceutical product containing omega-3-acid ethyl esters, namely Omacor Capsules 1000mg (HK-66442). The product is registered by Lee's Pharmaceutical (HK) Limited. It is a prescription-only medicine. As of the end of September 2023, the Department of Health (DH) had not received any case of adverse drug reaction related to omega-3-acid ethyl esters. In light of the above EMA's announcement, the DH issued letters to inform local healthcare professionals to draw their attention on 3 October 2023, and the matter will be discussed by the Registration Committee of the Pharmacy and Poisons Board.

Drug Recall

Batch recall of Allergenic Extract for diagnostic test – Pecan Nut (Food)

On 5 September 2023, the Department of Health (DH) endorsed licensed wholesaler, Ksena Healthcare Limited (Ksena), to recall a batch (lot number 0003963971) of skin test reagent for allergy to pecan nut, namely Allergenic extract – Pecan Nut (Food) due to potential quality issue.

The DH received notification from Ksena that the overseas manufacturer has recalled the skin test reagent due to reports of individuals who were test-negative using the above product lot subsequently experienced allergic reactions to pecan nut. As a precautionary measure, Ksena voluntarily recall the affected batch. DH's investigation is continuing.

The above product is a skin test reagent for allergy to pecan nut, the product was unregistered but imported for the treatment of particular patient by registered medical practitioner through Ksena.

As of the end of September 2023, the DH had not received any adverse reaction reports in connection with the above batch of product. A recall notice was posted in the Drug Office website on 5 September 2023 to alert the public of the product recall. The DH will closely monitor the recall.

Batch recall of Esopam 10 Tablets 10mg

On 12 September 2023, the Department of Health (DH) endorsed a licensed drug wholesaler, Health Alliance International Co. Ltd (Health Alliance), to recall a batch (batch number: 2OL201) of Esopam 10 Tablets 10mg (Hong Kong registration number: HK-65913) from the market due to potential quality issue.

The DH received notification from Health Alliance indicating that they were informed by the overseas manufacturer that product sample failed the tablet's dissolution test, which might affect the efficacy of the products. As a precautionary measure, Health Alliance is voluntarily recalling the product of concerned batch from the market.

The above product, containing escitalopram, is a prescription-only medicine indicated for depressive illness and generalized anxiety disorder. According to Health Alliance, the above batch of product has only been supplied to local private doctors and pharmacies, and it was not exported outside Hong Kong.

As of the end of September 2023, the DH had not received any adverse drug reaction report related to the affected batch of product. A recall notice was posted in the Drug Office website on 12 September 2023 to alert the public of the product recall. The DH will closely monitor the recall.

Drug Incident

Man arrested for suspected illegal sale and possession of slimming product with undeclared controlled drug ingredients including banned drug ingredient

On 22 September 2023, the Department of Health (DH) conducted an operation against the sale of a slimming product, namely VSlimming Herbal, which was found to contain undeclared controlled drug ingredients, including a banned drug ingredient. During the operation, a 36-year-old man was arrested by the Police for suspected illegal sale and possession of Part 1 poisons and an unregistered pharmaceutical product.

Acting upon intelligence, a sample of the above suspected unregistered pharmaceutical product was purchased from a retail store in Sham Shui Po for analysis. Test results from the Government Laboratory revealed that the oral capsules included in the sample contained sibutramine, N-desmethylsibutramine and spironolactone, all of which are Part 1 poisons under the Pharmacy and Poisons Ordinance (Cap. 138) (the Ordinance). 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. Spironolactone is a prescription drug used in the management of heart failure and should only be used under supervision of a doctor. Side effects include headaches, gastrointestinal disturbance, hyponatraemia (abnormally low blood sodium level) and hyperkalaemia (elevated blood potassium level).

A press release was posted in the Drug Office website on 22 September 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,
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.