Drug News
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This is a monthly digest of local and overseas drug safety news released by the Drug Office of the Department of Health in December 2021 with relevant information update before publish. For the latest news and information, please refer to public announcements or the website of the Drug Office of the Department of Health (http://www.drugoffice.gov.hk).

Safety Update

European Union: PRAC update on risk of myocarditis and pericarditis with mRNA vaccines

On 3 December 2021, the European Medicines Agency (EMA) announced that their safety committee (PRAC) has assessed recent data on the known risk of myocarditis and pericarditis following vaccination with COVID-19 vaccines Comirnaty and Spikevax (previously COVID-19 Vaccine Moderna). This review included two large European epidemiological studies. One study was conducted using data from the French national health system (Epi-phare) and the other one was based on Nordic registry data.

Overall, the outcome of the review confirms the risk of myocarditis and pericarditis, which is already reflected in the product information for these two vaccines, and provides further details on these two conditions.

Based on the reviewed data, the PRAC has determined that the risk for both of these conditions is overall "very rare", meaning that up to one in 10,000 vaccinated people may be affected. Additionally, the data show that the increased risk of myocarditis after vaccination is highest in younger males.

The PRAC has recommended updating the product information accordingly.

Myocarditis and pericarditis can develop within just a few days after vaccination, and have primarily occurred within 14 days. They have more often been observed after the second vaccination.

The French and Nordic studies provide estimates of the number of extra cases of myocarditis in younger males following the second dose, compared to unexposed persons of the same age and gender.

For Comirnaty, the French study shows that, in a period of seven days after the second dose, there were about 0.26 extra cases of myocarditis in 12- to 29-year-old males per 10,000 compared to unexposed persons. In the Nordic study, in a period of 28 days after the second dose, there were 0.57 extra cases of myocarditis in 16- to 24-year-old males per 10,000 compared to unexposed persons.

In the case of Spikevax, the French study showed that in a period of seven days after the second dose there were about 1.3 extra cases of myocarditis in 12- to 29-year-old males per 10,000 compared to unexposed persons. The Nordic study shows that in a period of 28 days after the second dose of Spikevax there were around 1.9 extra cases of myocarditis in 16- to 24-year-old males per 10,000 compared to unexposed persons.

Myocarditis and pericarditis are inflammatory conditions of the heart that present a range of symptoms, often including breathlessness, a forceful heartbeat that may be irregular (palpitations), and chest pain. Available data suggest that the course of myocarditis and pericarditis following vaccination is not different from myocarditis or pericarditis in general.

EMA will continue to closely monitor this issue and will communicate further when new information becomes available. EMA confirms that the benefits of all authorised COVID-19 vaccines continue to outweigh their risks, given the risk of COVID-19 illness and related complications, and as scientific evidence shows that they reduce deaths and hospitalisations due to COVID-19.

In Hong Kong, the above products are not registered pharmaceutical products under the

Pharmacy and Poisons Ordinance (Cap. 138). The COVID-19 vaccine by Fosun Pharma/BioNTech (i.e. Comirnaty) is authorised for emergency use in Hong Kong in accordance with the Prevention and Control of Disease (Use of Vaccines) Regulation (Cap. 599K). The package insert of Comirnaty has already been updated to include myocarditis and pericarditis as its adverse reactions. Related news was previously issued by various overseas drug regulatory authorities, and was reported in Drug News Issues Nos. 140, 141 and 144. The Department of Health (DH) issued letters to inform local healthcare professionals to draw their attention on 28 June 2021. The DH will remain vigilant on any safety update of the product issued by other overseas drug regulatory authorities.

Australia: Rifampicin - Low levels of contamination with 1-methyl-4-nitrosopiperazine

On 7 December 2021, the Therapeutic Goods Administration (TGA) announced that it is investigating potential contamination of rifampicin medicines with very low levels of the nitrosamine impurity, 1-methyl-4-nitrosopiperazine (MeNP or MNP).

Rifampicin is an antibiotic prescription medicine. Rifampicin is an essential, first-line medicine for the treatment of tuberculosis. Rifampicin is also used to treat or prevent other serious infections.

Australian sponsors of rifampicin products have reported that all rifampicin products in the Australian market contain traces of MeNP. This issue also affects rifampicin products supplied internationally.

Consumers are strongly advised to continue to take their rifampicin medicines as prescribed. It is critical that patients do not stop taking their rifampicin medicines unless instructed to by their health professional.

MeNP is a type of nitrosamine that is present as an impurity. Nitrosamines are a group of compounds which can damage DNA. They are commonly found in low levels in a variety of foods, including smoked and cured meats, dairy products, vegetables, in some drinking water, and in air pollution. Long-term exposure, over years, can increase an individual's risk of developing cancer.

The additional risk that would be posed by the trace levels of MeNP being detected in rifampicin is likely to be very low. However, the presence of nitrosamine impurities is generally considered unacceptable for a medicine. The actual health risk depends on the medicine and dose taken and will vary from person to person.

Health professionals should be aware that MeNP is present at very low levels in rifampicin products supplied in Australia. However, there is no reason to stop prescribing rifampicin as the benefits continue to far outweigh the risk posed by this impurity. Health professionals may wish to remind patients of the importance of treating tuberculosis and to continue taking their medicines in line with the instructions in the product information. Patients should be reassured that that the risks posed by MeNP at the trace levels observed overseas are considered very low.

The TGA has reviewed results reported by sponsors of rifampicin medicines on the Australian Register of Therapeutic Goods. The TGA continues to work with its international regulatory partners and rifampicin sponsors to respond to this issue. Consistent with international regulatory approaches including in Europe and the Unites States, the TGA is allowing sponsors to supply rifampicin products with trace amounts of MeNP to the Australian market to ensure that patients have continued access to this essential medicine.

In Hong Kong, there are 24 registered pharmaceutical products containing rifampicin. All products are prescription-only medicines. Related news was previously issued by the United States Food and Drug Administration and Singapore Health Sciences Authority, and was reported in Drug News Issues Nos. 130 and 138 respectively. As of the end of December 2021, the Department of Health (DH) has received 22 cases of adverse drug reaction related to rifampicin. None of them is concluded to be related to the presence of 1-methyl-4-nitrosopiperazine (MNP).

The DH has contacted the certificate holders of all registered rifampicin products for follow up on the local impact of the issue and to provide evidence that MNP in the products are below acceptance limit. When any health risks are posed to the public, a press statement will be issued as soon as possible. The DH will remain vigilant on the development of the issue and any safety update of the drug issued by overseas drug regulatory authorities for consideration of any action deemed

necessary.

Canada: Summary Safety Review: Aimovig (erenumab) - Assessing the potential risks of non-fatal stroke, non-fatal heart attack and cardiovascular death

On 8 December 2021, Health Canada announced that it reviewed the potential risks of non-fatal stroke, non-fatal heart attack and cardiovascular death with the use of Aimovig. This safety review was triggered by new information from safety reports, related to these potential risks, received from the manufacturer.

A stroke happens when the blood supply to part of the brain is stopped or lowered, blocking brain tissue from getting enough oxygen and nutrients, leading to the death of brain cells. A heart attack happens when blood flow, bringing oxygen and nutrients, to the heart muscle is lowered or cut off completely. The heart muscle may be damaged, and heart function could be weakened. Depending on the extent of the brain or heart tissue injury, there could be long-term health consequences or cardiovascular death in rare situations.

Erenumab, the active ingredient in Aimovig, is a monoclonal antibody that blocks the function of a protein called calcitonin gene-related peptide that can cause a migraine.

Health Canada reviewed information received from the manufacturer, and information from searches of the Canada Vigilance database, international databases, and published literature. Health Canada considered 196 case reports (134 international and 62 Canadian) for this safety review. Ten cases (all Canadian) met the criteria for further assessment to determine if there was a link between Aimovig use and the risk of non-fatal stroke, non-fatal heart attack or cardiovascular death. Health Canada's assessment of the 10 Canadian cases could not confirm a link between the use of Aimovig and non-fatal stroke, non-fatal heart attack, or cardiovascular death. These cases either included factors such as other medications taken by the patients or medical conditions that may have contributed to these risks, or contained insufficient medical information. At the time of the review, Health Canada did not find any reports in the scientific literature to support a link between non-fatal stroke, non-fatal heart attack or cardiovascular death and Aimovig use.

Health Canada's review of the available information could not confirm a link between the use of Aimovig and non-fatal stroke, non-fatal heart attack or cardiovascular death. Health Canada will continue to monitor the safety of Aimovig, as it does for all health products on the Canadian market.

In Hong Kong, there are 2 registered pharmaceutical products containing erenumab, namely Aimovig Solution For Injection in Pre-filled Pen 70mg/ml (HK-66406) and Aimovig Solution For Injection in Pre-filled Pen 140mg/ml (HK-66847). Both products are registered by Novartis Pharmaceuticals (HK) Limited. They are prescription-only medicines. As of the end of December 2021, the Department of Health (DH) has received 3 cases of adverse drug reaction related to erenumab, but these cases were not related to non-fatal stroke, non-fatal heart attack or cardiovascular death. The DH will remain vigilant on any safety update of the drug issued by other overseas drug regulatory authorities.

The United Kingdom: Dapagliflozin (Forxiga) - no longer authorised for treatment of type 1 diabetes mellitus

On 10 December 2021, Medicines and Healthcare products Regulatory Agency (MHRA) announced that the authorisation holder for dapagliflozin has withdrawn the indication for type 1 diabetes mellitus. The removal of the type 1 diabetes indication is not due to any new safety concerns and the other indications of dapagliflozin are unchanged.

Sodium glucose co-transporter 2 (SGLT2) inhibitors act to improve glycaemic control by reducing glucose reabsorption and increasing urinary glucose excretion. The SGLT2 inhibitor dapagliflozin has been indicated for the treatment of type 2 diabetes since 2012 and is also indicated in adults for the treatment of symptomatic chronic heart failure with reduced ejection fraction and for the treatment of chronic kidney disease. Dapagliflozin (Forxiga) was authorised in 2019 as an adjunct to insulin in patients with type 1 diabetes with a body-mass index (BMI) of 27 kg per m2 or higher, when insulin alone does not provide adequate glycaemic control despite optimal insulin therapy.

On 25 October 2021, the marketing authorisation holder for dapagliflozin withdrew the indication for

type 1 diabetes across Europe and in the UK. A letter was sent to UK healthcare professionals to inform them of the withdrawal. As such, patients with type 1 diabetes should discontinue dapagliflozin 5mg in consultation with their specialist diabetes physician as soon as clinically practical.

Dapagliflozin has a diuretic effect and has been associated with a decrease in blood pressure. It should therefore be noted that a small increase in blood pressure may be seen upon discontinuation of dapagliflozin.

Dapagliflozin was the only SGLT2 inhibitor that was available for treatment of type 1 diabetes. The use of dapagliflozin 5mg for the treatment of type 1 diabetes required specific additional risk minimisation measures for the risk of diabetic ketoacidosis, including a patient alert card and a healthcare professional guide. This reflected the increased risk in type 1 compared with type 2 diabetes, with studies in type 1 diabetes reporting diabetic ketoacidosis with a common frequency (may affect up to 1 in 10 patients), and cases reported of euglycaemic diabetic ketoacidosis. As a result of the indication removal, the additional risk minimisation materials are no longer available.

The decision by the marketing authorisation holder to voluntarily withdraw the indication in type 1 diabetes followed commercial considerations due to a specific European-wide regulatory requirement for this authorisation. The decision was not driven by any new safety concerns, such as the already known increased risk of diabetic ketoacidosis in type 1 diabetes compared with type 2 diabetes.

Other indications for dapagliflozin 5mg and 10mg are not affected by this licensing change and both strengths will remain on the market.

In Hong Kong, there are 5 registered pharmaceutical products containing dapagliflozin. All these products are prescription only medicines and have not registered for the indication of treatment of type 1 diabetes mellitus. In light of the above MHRA announcement, the Department of Health (DH) will remain vigilant on any safety update of the drugs issued by other overseas drug regulatory authorities.

Canada: Summary Safety Review: Amoxicillin-containing products - Assessing the potential risks of Aseptic meningitis

On 10 December 2021, Health Canada announced that it reviewed the potential risk of aseptic meningitis in patients treated with amoxicillin-containing products. The safety review was triggered by case reports published in the literature in the past 3 years concerning this risk.

Health Canada reviewed the available information from searches of the Canada Vigilance database, international databases, and published literature and concluded that there may be a link between the use of amoxicillin-containing products and the risk of aseptic meningitis. Health Canada will work with the manufacturers to include the risk of aseptic meningitis in the Canadian Product Monographs for amoxicillin-containing products that do not already contain this safety information.

In Hong Kong, there are 180 registered pharmaceutical products containing amoxicillin for human use and are prescription-only medicines. As of the end of December 2021, the Department of Health (DH) has received 28 cases of adverse drug reaction related to amoxicillin, but these cases are not related to aseptic meningitis. In light of the above Health Canada's announcement, the DH issued letters to inform local healthcare professionals to draw their attention on 13 December 2021. The DH will remain vigilant on any safety update of the drug issued by other overseas drug regulatory authorities.

Singapore: Allopurinol-induced severe cutaneous adverse reactions and the role of HLA-B*5801 genotyping - a reminder

On 21 December 2021, Health Sciences Authority (HSA) issued an announcement to remind healthcare professionals about the risk of severe cutaneous adverse reactions (SCAR) with the use of allopurinol and the role of HLA-B*5801 genotyping prior to therapy initiation.

In March 2016, the Ministry of Health (MOH) and HSA jointly issued a Dear Healthcare Professional Letter to inform that HLA-B*5801 genotyping prior to the initiation of allopurinol therapy is not required as standard of care. Nonetheless, healthcare professionals were also advised that they may consider genotyping patients who have pre-existing risk factors for allopurinol-induced SCAR such as renal impairment and older age, to identify those who are at a greater risk of allopurinol-induced SCAR.

From March 2016 to 1 October 2021, HSA has received 80 cases of allopurinol-induced SCAR, such as Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) and drug reaction with eosinophilia and systemic symptoms (DRESS). Six of these cases were fatal. Allopurinol was the sole suspected agent in majority (n=69, 86%) of the cases. Notably, most of the cases had risk factors for SCAR, such as older age and renal impairment. Of the 71 cases with age reported, close to two-thirds (65%) were aged 60 years and above. Renal function was reported in 42 cases, of which approximately two-thirds (64%) had renal impairment. Of the 41 cases where allopurinol dose was reported, nearly two-thirds (63%) received allopurinol 100mg or below daily while the remaining cases received daily doses ranging from more than 100mg to 300mg.

Information on when the HLA-B*5801 genotyping test was conducted, and the corresponding test results were available for 12 cases and 14 cases respectively. The majority of the cases were tested following the development of SCAR (71%) and were HLA-B*5801 positive (86%). Most of the HLA-B*5801-positive cases were aged 60 years and above (92%) and/or reported renal impairment of varying degrees (~67%). The remaining two HLA-B*5801-negative cases were aged 60 years and above and had chronic kidney disease.

The HLA-B*5801 genotyping test has high sensitivity and selectivity of over 80% for allopurinol-induced SCAR. However, the rarity of allopurinol-induced SCAR (i.e. around 3 out of 1,000 patients on allopurinol may develop SCAR) leads to a low positive predictive value (PPV) of the HLA-B*5801 test (estimated PPV: 2%, i.e. approximately 2 out of 100 HLA-B*5801-positive people starting allopurinol may develop SCAR). The low PPV, together with a lack of alternative cost-effective urate-lowering therapy options, limit the overall value of routine genotyping from a health-systems perspective. Testing for the allele may be more useful in treatment decision-making if the patient is assessed to already be at a higher risk of allopurinol-induced SCAR with renal impairment or older age.

Healthcare professionals are reminded of the following advisory, when considering the use of allopurinol in new patients:

- Allopurinol should be used with caution especially in older patients with renal impairment. Consider starting at a low dose and titrate accordingly.
- While HLA-B*5801 genotyping is not routinely recommended for new patients initiating allopurinol, healthcare professionals may consider genotyping patients who have pre-existing risk factors for allopurinol-induced SCAR such as renal impairment and older age, to identify those who are at a greater risk of allopurinol-induced SCAR. While patients who have tested negative for the HLA-B*5801 allele are at lower risk of developing allopurinol-induced SCAR, they can still develop SCAR as there are non-genetic factors that increase the risk. Hence, genetic testing, when ordered for at-risk patients, should not substitute for appropriate clinical vigilance and patient management.
- Healthcare professionals are advised to consider and discuss with their patients the benefits of treatment with allopurinol and its risks, including SCAR, as well as the availability of pre-treatment HLA-B*5801 genotyping test before prescribing allopurinol.
- Healthcare professionals are also advised to educate patients on the recognition of early signs and symptoms of SCAR and the importance of prompt drug withdrawal and medical consultation at the first sign of rash.

In Hong Kong, there are 37 registered pharmaceutical products containing allopurinol. As of the end of December 2021, the Department of Health (DH) has received 4 cases of adverse drug reaction related to allopurinol, of which 3 cases were related to SJS and one case was related to TEN and DRESS. Related news was previously issued by HSA and was reported in Drug News Issues No. 77. Currently, the label and/or package insert of locally registered pharmaceutical products containing allopurinol should contain relevant safety warning, e.g. “Allopurinol should be discontinued at the first appearance of skin rash or other signs which may indicate an allergic reaction. In some instances, a skin rash may be followed by more severe reactions such as exfoliative, urticarial and purpuric lesions as well as Stevens-Johnson syndrome”. The DH will remain vigilant on any safety update of the drug issued by other overseas drug regulatory authorities.

Canada: Summary Safety Review: Domperidone - Assessing the potential risks of serious ventricular arrhythmias, QT interval prolongation and sudden cardiac death

Safety Update

On 30 December 2021, Health Canada announced that it carried out a follow-up safety review of domperidone and serious ventricular arrhythmia, QT interval prolongation and sudden cardiac death in 2021 to one previously completed in 2014. This latest safety review was triggered by the publication of a Canadian study on the risk of heart effects with domperidone when used for lactation promotion, an off-label use in Canada. The purpose of the current review was to consider recent information, for both the approved and off-label use, and determine if additional measures were warranted.

Health Canada reviewed the available information from searches of the Canada Vigilance database and published literature for both the approved and off-label use of domperidone. Health Canada reviewed 15 cases (8 Canadian and 7 international) of serious ventricular arrhythmia, QT interval prolongation, and/or sudden cardiac death/cardiac arrest following the use of domperidone for both the approved and off-label use. Of the 15 cases, 6 (3 Canadian) were found to have a possible link with domperidone use. The remaining 9 cases (3 Canadian) did not have enough information to be further assessed.

The Canadian study that triggered this review found that the risk of cardiac side effects is very low in individuals using domperidone off-label to promote lactation. Health Canada's safety review also looked at the scientific literature published since 2014, and did not find any new information about serious ventricular arrhythmia, QT interval prolongation, or sudden cardiac death following the use of domperidone for both the approved and off-label use.

Health Canada's review of the available information found no new safety information related to the risks of serious ventricular arrhythmia, QT interval prolongation or sudden cardiac death for both the approved and off-label use of domperidone. As a result, no further updates to the Canadian Product Monographs are warranted.

In Hong Kong, there are 41 registered pharmaceutical products containing domperidone. All products are prescription-only medicines. As of the end of December 2021, the Department of Health (DH) has not received any case of adverse drug reaction related to domperidone.

News related to risk of serious cardiac adverse drug reactions associated with the use of domperidone was previously issued by various overseas drug regulatory authorities, and was reported in Drug News Issues Nos. 29, 53, 59, 63, 91 and 122.

The Department of Health (DH) issued letters to inform local healthcare professionals to draw their attention on 8 March 2012, 10 March 2014, 19 April 2016 and 17 December 2019. In February 2012, May 2014 and June 2020, the Registration Committee of the Pharmacy and Poisons Board discussed the matter and decided that the sales pack label and/or package insert of domperidone-containing products should include the appropriate safety information related to cardiovascular risks. The DH will remain vigilant on any safety update of the drug issued by other overseas drug regulatory authorities.

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.

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:

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Adverse Drug Reaction (ADR) Reporting:

Tel: 2319 2920
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Link: http://www.drugoffice.gov.hk/adr.html

Post: Adverse Drug Reaction and Adverse Event Following Immunization Unit,
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The purpose of Drug News is to provide healthcare professionals with a summary of local and overseas drug safety news released. Healthcare professionals are advised to keep update with the information and provide corresponding advice or therapeutic measure to patients and public.