Drug News
藥 物 情 報

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This is a monthly digest of local and overseas drug safety news released by the Drug Office of the Department of Health in August 2022 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

Canada: Summary Safety Review: Nexavar (sorafenib): Assessing the potential risk of thrombotic microangiopathy

On 11 August 2022, Health Canada announced that it reviewed the potential risk of thrombotic microangiopathy (TMA) with the use of Nexavar. This safety review was triggered by a United States Food and Drug Administration update to the product safety information for Nexavar to include the risk of TMA, as well as international case reports published in the medical literature.

TMA is a group of rare, but serious and life-threatening conditions, involving the formation of clots in the small blood vessels. These clots can cause damage to organs and body systems by blocking proper blood flow. TMA is a medical emergency and requires rapid intervention. A number of factors, including congenital conditions (those present at birth), infection, cancer and drugs, can cause TMA.

Health Canada reviewed information provided by the manufacturer, and information resulting from searches of the Canada Vigilance database and the published literature. Health Canada reviewed 28 cases (1 Canadian, 27 international) of TMA in patients taking Nexavar. Of the 28 cases, 12 (all international) met the criteria for further assessment to determine if there was a link between the use of Nexavar and TMA. All 12 cases, including 6 published in the scientific literature, were found to be possibly linked to the use of Nexavar. Three deaths were reported (2 of which were assessed as having a possible link to Nexavar and 1 unlikely to be linked). There were no Canadian cases of TMA found to be linked to the use of Nexavar.

Health Canada's review of the available information concluded that there may be a link between the use of Nexavar and the risk of TMA. Health Canada will work with the manufacturer to update the Canadian product monograph for Nexavar to include the risk of TMA.

In Hong Kong, there are 2 registered pharmaceutical products containing sorafenib. Both products are prescription-only medicines. As of the end of August 2022, the Department of Health (DH) had received 18 cases of adverse drug reaction related to sorafenib, but these cases were not related to TMA. In light of the above Health Canada's announcement, the DH issued letters to inform local healthcare professionals to draw their attention on 12 August 2022, and the matter will be discussed by the Registration Committee of the Pharmacy and Poisons Board.

Canada: Imbruvica (ibrutinib): Risk of serious and fatal cardiac arrhythmias or cardiac failure

On 29 August 2022, Health Canada announced that serious and fatal events of cardiac arrhythmia or cardiac failure have occurred in patients treated with Imbruvica. Patients with significant cardiac co-morbidities may be at greater risk for developing these events, including sudden fatal cardiac events. Related warnings have been in the Canadian Product Monograph (CPM) since authorization.

Responding to data from new clinical trials and ongoing monitoring of product safety, the CPM for Imbruvica has been updated to include stronger warnings on these cardiac-related events and new dose modification guidelines.

Among the 4,896 patients who received Imbruvica in clinical trials, which included patients who received Imbruvica in unapproved monotherapy or combination regimens, cardiac-related deaths or sudden deaths were reported in 1% of patients. Of

the 4,896 patients, 0.2% reported Grade ≥3 ventricular tachyarrhythmias, 3.7% reported Grade ≥3 atrial fibrillation and atrial flutter, and 1.3% reported Grade ≥3 cardiac failure. These events occurred particularly in patients with acute infections or cardiac risk factors including hypertension, diabetes mellitus and a previous history of cardiac arrhythmia.

New guidelines for Imbruvica dose modification or treatment discontinuation due to cardiac arrhythmia or cardiac failure have been added to the Imbruvica CPM. These dose modification guidelines are intended to improve tolerability for continued Imbruvica treatment and may reduce the occurrence of additional serious events.

Healthcare professionals are advised to:

- Clinically evaluate patients' cardiac function and consider cardiac history prior to initiating Imbruvica therapy.
- Closely monitor patients for clinical signs of cardiac function deterioration during treatment, and manage appropriately. Consider further evaluation (e.g., electrocardiogram, echocardiogram) for patients who develop arrhythmic symptoms (e.g., palpitations, light-headedness) or new onset of dyspnea.
- Follow the new dose modification guidelines for patients with new onset or worsening cardiac arrhythmia or cardiac failure.

Janssen Inc., in collaboration with Health Canada, has updated the CPM for Imbruvica to include new warnings regarding serious and fatal events of cardiac arrhythmia or cardiac failure, including new dose modification guidelines.

In Hong Kong, there are 4 registered pharmaceutical products containing ibrutinib, namely Imbruvica Capsules 140mg (HK-64088), Imbruvica Capsules 140mg (HK-65397), Imbruvica Tablets 140mg (HK-67062) and Imbruvica Tablets 280mg (HK-67063). All products are registered by Johnson & Johnson (Hong Kong) Ltd. They are prescription-only medicines. As of the end of August 2022, the Department of Health (DH) had received 27 cases of adverse drug reaction related to ibrutinib, of which 5 cases were related to atrial fibrillation and one case was related to heart failure.

Related news on the risk of ventricular tachyarrhythmia associated with the use of ibrutinib was previously issued by the United Kingdom Medicines and Healthcare products Regulatory Agency and Health Canada, and was reported in Drug News Issues No. 94 and 105. The DH issued letters to inform local healthcare professionals to draw their attention on 16 August 2017. In December 2017, the Registration Committee of the Pharmacy and Poisons Board discussed the matter and decided that the package insert of ibrutinib-containing products should include safety information on the risk of ventricular tachyarrhythmia.

The current package insert of the above 4 local ibrutinib-containing products include safety information on the risk of cardiac arrhythmia (including atrial fibrillation, atrial flutter and ventricular tachyarrhythmia) and cardiac failure. 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.

Singapore: QT prolongation and Torsades de Pointes with donepezil

On 30 August 2022, Health Sciences Authority (HSA) announced that cases of QT prolongation and Torsades de Pointes (TdP) associated with donepezil have been reported overseas and in published literature.

Kho et al. conducted a single-centre retrospective analysis to investigate the effect of long-term donepezil therapy on electrocardiogram (ECG) changes, in particular its effects on the QT interval. A resting 12-lead ECG obtained during the most recent acute hospital admission was compared to the ECG prior to commencing donepezil therapy. Fifty-nine patients who were on donepezil therapy for at least a year and 53 controls (matched for age, gender, ethnicity and comorbidities) were included in the study. The study found that long-term use of donepezil (≥1 year) was associated with significantly prolonged QT intervals (393.3 ± 35.6ms at baseline vs 411.9 ± 44.6ms on donepezil; p=0.002), and the results remained consistent across the QT corrected using Bazett (QTcB), Fredericia, Framingham and Hodges formulae. Among those treated with donepezil, 16 male and 11 female patients presented with QT prolongation, defined in the study as QTcB interval ≥450ms and ≥460ms respectively, with the longest QTcB interval at 570ms. Of these patients, 11 males and five females had normal corrected QT intervals prior to starting treatment. In contrast, no cases of QT prolongation nor any significant

changes to the QT intervals were noted in the control group (393.3 ± 36.1ms vs 387.4 ± 37.0ms; p=0.156). Donepezil was also found to increase the PR (177.0 ± 29.0ms vs 186.1 ± 34.2ms; p=0.04) and QRS (101.7 ± 20.3ms vs 104.7 ± 22.3ms; p=0.04) intervals, but no dose- or treatment duration-related differences were observed. Based on their findings, the authors recommended that ECG evaluation should take place before and after donepezil initiation.

In July 2021, the European Medicines Agency (EMA) assessed that donepezil may increase the risk of cardiac conduction disorders including QT prolongation and TdP. The review considered information from spontaneous adverse event reports and published literature. The EMA recommended for the addition of warnings on QT prolongation and TdP and interactions with other medicinal products known to prolong the QT interval to the package inserts (PIs) of donepezil products. Similar updates on cardiac conduction disorders were made to the Australian PIs for donepezil following the Australian Therapeutic Goods Administration's (TGA) review of evidence from published literature and domestic and international post-market adverse event data.

To date, HSA has not received any local reports of QT prolongation or TdP associated with donepezil. HSA is in the process of working with the product registrants to include warnings on QT prolongation and TdP in the local PIs of donepezil products. Healthcare professionals are advised to consider the risk of QT prolongation or TdP when prescribing donepezil to patients with pre-existing or family history of QT prolongation, relevant pre-existing cardiac disease (e.g., decompensated heart failure, recent myocardial infarction, bradyarrhythmias), electrolyte disturbances (hypokalaemia, hypomagnesaemia), or taking concomitant drugs known to affect the QT interval. They may wish to consider ECG evaluation as part of the clinical monitoring of at-risk patients.

In Hong Kong, there are 35 registered pharmaceutical products containing donepezil. All products are prescription-only medicines. As of the end of August 2022, the Department of Health (DH) had not received any case of adverse drug reaction related to donepezil.

Related news was previously issued by TGA and Health Canada, and was reported in Drug News Issues No. 148 and 153. The DH issued letters to inform local healthcare professionals to draw their attention on 1 March 2022 and 20 July 2022. As previously reported, the matter will be discussed by the Registration Committee of the Pharmacy and Poisons Board .

Singapore: Finasteride and potential risk of suicidal ideation

On 30 August 2022, Health Sciences Authority (HSA) announced that a recent pharmacovigilance study by Nguyen et al. suggested that younger patients with alopecia may be more vulnerable to the risk of suicidality, although this association might be biased by stimulated reporting.

In the study, disproportionality analysis was used to assess whether suicidality or psychological adverse events (AEs) were more frequently reported for finasteride than would be expected by chance alone by comparing them against similar reports for all other drugs in VigiBase, the World Health Organisation's global safety database. The study identified 356 reports of suicidality (suicidal ideation, attempted suicide, or completed suicide) and 2,926 reports of psychological AEs (depression or anxiety) in users of finasteride, reported from 1993 to 2019. Among the reports with data available, the majority (99%) occurred in males, and 71% occurred in individuals aged between 18 and 44 years. Significant disproportionality signals for suicidality (reporting odds ratio [ROR], 1.63; 95% CI, 1.47-1.81) and psychological AEs (ROR, 4.33; 95% CI, 4.17-4.49) were identified in finasteride users. In addition, when stratified by age and indication, younger patients less than 45 years old (ROR 3.47, 95% CI 2.90-4.15) and patients with alopecia (ROR 2.06, 95% CI 1.81-2.34) had significant disproportionality signals for suicidality that were not present in older patients or patients with benign prostatic hyperplasia. Conversely, this disproportionality in reporting of suicidality or psychological AEs was not observed for drugs with similar indications but different mechanisms of action (tamsulosin and minoxidil) or similar mechanisms of action and AE profiles (dutasteride). The study also found that suicidality and psychological AE reports were highest in 2015 to 2019 (81.5% and 78.8%, respectively). Sensitivity analyses showed a disproportionate signal of reporting after the year 2012 (ROR, 2.13; 95% CI, 1.91-2.39), following widespread publicisation of a potential link between finasteride and psychological morbidity. This suggests a reporting bias of stimulated reporting during these

years that merits further investigation.

In 2019, Health Canada completed its latest safety review on the risk of suicidal thoughts and/or behaviour in response to reported domestic and international cases of suicidal ideation and self-injury. While the international reports, literature, and regulatory information reviewed could neither confirm nor deny a causal relationship between finasteride and suicide/self-injury, Health Canada concluded that there may be a link between finasteride and the risk of suicidal ideation and updated the Canadian product information to include a warning on this potential safety issue. Similar product information updates had also been implemented by the Australian Therapeutic Goods Administration, the European Medicines Agency, the United Kingdom's Medicines and Healthcare products Regulatory Agency (MHRA) and the United States' Food and Drug Administration.

To date, HSA has received one report in 2014 of a 19-year-old male who developed severe mental depression with suicidal tendency after one month's use of finasteride 1mg. The patient recovered fully several weeks after stopping the medication. The local package inserts of finasteride-containing products currently list depression and suicidal ideation as psychiatric AEs observed post-market. Mood alterations including depression and, less frequently, suicidal ideation have been reported in patients treated with finasteride. Healthcare professionals are advised to consider the potential risk of psychological AEs when assessing the benefit-risk of finasteride for their patients.

In Hong Kong, there are 32 registered pharmaceutical products containing finasteride. All products are prescription-only medicines. As of the end of August 2022, the Department of Health (DH) had received 4 cases of adverse drug reaction related to finasteride, of which one case was related to depression.

Related news was previously issued by MHRA and Health Canada, and was reported in Drug News Issues No. 91 and 112. The DH issued letters to inform local healthcare professionals to draw their attention on 25 May 2017. In September 2017, the Registration Committee of the Pharmacy and Poisons Board discussed the matter and decided that the sales pack label and/or package insert of finasteride-containing products should include safety information on mood alterations (including depression and suicidal ideation). The DH will remain vigilant on safety update of the drug issued by other overseas drug regulatory authorities.

Singapore: Selective serotonin reuptake inhibitors and risk of suicidality

On 30 August 2022, Health Sciences Authority (HSA) announced that selective serotonin reuptake inhibitors (SSRIs) are known to be associated with an age-dependent risk of suicidality, where an increased risk is observed particularly in patients less than 25 years of age. However, the causal association remains to be conclusively established, as the risk of suicidality may be confounded by the patient's underlying psychiatric condition and its severity.

A meta-analysis of 24 short-term placebo-controlled trials of major depressive disorder (MDD) or other psychiatric disorders involving over 4,400 children and adolescents found a greater risk of suicidal ideation and behaviour (but not completed suicide) during the first few weeks after treatment initiation with SSRIs as compared with placebo (4% vs 2%; risk ratio 1.95, 95% confidence interval [CI] 1.28 to 2.98). Similarly, another pooled analysis of 295 short-term (median duration 2 months) placebo-controlled trials of 11 antidepressant drugs, of which the majority were SSRIs, in over 77,000 adults with MDD or other psychiatric disorders found a higher risk of suicidal behaviour associated with antidepressant use among patients less than 25 years old (odds ratio [OR] 2.30, 95% CI 1.04 to 5.09). However, no increased risk was observed in adults aged 25 to 64 years (OR 1.03, 95% CI 0.68-1.58) and a risk reduction was observed in adults aged 65 years old or greater (OR 0.06, 95% CI 0.01-0.58).

In Singapore, the registered SSRIs include escitalopram, fluoxetine, fluvoxamine, paroxetine and sertraline. They are mostly indicated for patients aged 18 years and above. Fluvoxamine is approved for use in children aged 8 years and above for the treatment of obsessive-compulsive disorder. Although none of the registered SSRIs are approved specifically for the treatment of depression in children and adolescents below 18 years old, they are used off-label in this patient population. Based on data from the electronic medical records, an average of 50,000 patients were prescribed SSRIs annually between 2017 and 2021. Of these patients, the majority were adults

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(≥25 years of age; 82.9%), followed by young adults (18-24 years; 13.5%) and children/adolescents (<18 years; 3.6%). Over those five years, an increasing trend in the prescriptions of SSRIs was observed. The increase ranged from 3.5% to 4.7% year-on-year from 2017 to 2020, followed by a bigger jump of 9.1% from 2020 to 2021. When analysed by age group, the annual proportion of children or adolescents prescribed SSRIs was stable at around 3.4% from 2017 to 2020 and increased to 4.1% in 2021, while those of young adults steadily increased over the years from 11.2% in 2017 to 15.5% in 2021. In contrast, there was a downward trend in the annual proportion of adults prescribed SSRIs from 85.4% in 2017 to 80.5% in 2021.

In Singapore, patient educational materials on SSRIs are available on publicly accessible platforms, including the Medication Information Leaflets (MILs) on HealthHub. These MILs, which were developed by the National Medication Information Workgroup with consensus from the College of Psychiatrists as well as the relevant chapter specialties of the College of Physicians, provide a brief overview on the uses of SSRIs and their side effects. The warnings on suicidality and mental state worsening in these MILs have recently been strengthened to highlight such risks in young people aged below 25 years and to improve patient awareness and education.

HSA, in consultation with its Product Vigilance Advisory Committee, has assessed that while warnings and advisories pertaining to suicidality risk have been highlighted in the local package inserts of SSRIs and patient educational materials, it would be relevant to remind healthcare professionals of SSRI-associated suicidality in young adults and the availability of MILs to aid patient counselling. This is in view of the increase in the use of SSRIs locally.

In Hong Kong, there are registered pharmaceutical products containing escitalopram (35 products), fluoxetine (22 products), fluvoxamine (4 products), paroxetine (8 products) and sertraline (20 products). All products are prescription-only medicines. As of the end of August 2022, the Department of Health (DH) had received adverse drug reaction related to escitalopram (2 cases), fluoxetine (21 cases; of which one case was related to suicide attempt in a 17 years old patient and one case was related to depressed mood in a 20 years old patient) and sertraline (5 cases). The DH had not received any case of adverse drug reaction related to fluvoxamine and paroxetine.

The risk of suicidal ideation associated with the use of SSRIs (including use in children, adolescents and young adults) 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.

Drug Recall

Batch Recall of "Sodium Chloride Injection 23.4% w/v"

On 3 August 2022, the Department of Health (DH) endorsed a licensed drug wholesaler, Sino-Asia Pharmaceutical Supplies Ltd. (Sino-Asia), to recall 5 batches (batch number: 0J970A, 1A106A, 1B134A, 1B142A & 1D191A) of Sodium Chloride Injection 23.4%w/v (Hong Kong registration number: HK-63077) from the market due to potential quality issue.

The DH received notification from Sino-Asia on 3 August 2022 that the overseas manufacturer of the product is initiating a voluntary recall of the above batches due to detection of glass particles in the product during stability test. As a precautionary measure, Sino-Asia is voluntarily recalling the affected products from the market.

The above product is a prescription medicine and is indicated as an additive in parenteral restoration of sodium ion in patients with restricted oral intake. According to Sino-Asia, the product has been imported into Hong Kong and supplied to the Hospital Authority, private hospitals and private medical practitioner.

As of the end of August 2022, the DH had not received any adverse reaction reports in connection with the products. A notice was posted on the Drug Office website on 3 August 2022 to alert the public of the product recall. The DH will closely monitor the recall.

Drug Incident

Public urged not to buy or use topical products containing undeclared controlled ingredient

On 23 August 2022, the Department of Health (DH) appealed to the public not to buy or use two topical products, ACH Cortizone EX Ultra Moisturizing Natural Herbs Anti-Itch Cream and ACH Cortizone EX Ultra Moisturizing Natural Herbs Anti-Itch Cream Natural plant, as they were found to contain an undeclared controlled drug ingredient.

Acting upon a public complaint, the DH purchased samples of the above two products for analysis. Test results from the Government Laboratory revealed that the product samples contained betamethasone dipropionate, which is a Part 1 poison under the Pharmacy and Poisons Ordinance (Cap 138). The products are also suspected to be unregistered pharmaceutical products.

The DH conducted an operation against a pharmacy in Tin Shui Wai on 23 August 2022, during which a 40-year-old man was arrested by the Police for suspected illegal sale of Part 1 poisons and unregistered pharmaceutical products. The DH's investigation is continuing.

Betamethasone dipropionate is a steroid substance for treating inflammation. Its side effects include moon face, high blood pressure, high blood sugar, skin atrophy, adrenal insufficiency and osteoporosis. Products containing betamethasone dipropionate are prescription medicines that should be used under a doctor's directions and be supplied in a pharmacy under the supervision of a registered pharmacist upon a doctor's prescription.

Upon completion of its investigation, the DH will seek advice from the Department of Justice on prosecution matters and will also refer the relevant case to the Board for consideration of possible disciplinary action.

A press release was posted on the Drug Office website on 23 August 2022 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.