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Prepared in collaboration with the WHO Collaborating Centre for International Drug Monitoring, Uppsala Sweden

The aim of the Newsletter is to disseminate information on the safety and efficacy of pharmaceutical products, based on communications received from our network of "drug information officers" and other sources such as specialised bulletins and journals, as well as partners in WHO.

The information is produced in the form of résumés in English, full texts of which may be obtained on request from:

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The WHO Pharmaceuticals Newsletter provides you with the latest information on the safety of medicines and legal actions taken by regulatory authorities across the world. It also includes write-ups on 'Signals' from Individual Case Safety Reports (ICSRs) available in the WHO Global ICSR database, VigiBase®.

This newsletter includes three feature articles describing: the 38th meeting of the WHO International Working Group for Drug Statistics Methodology; Pre-conference Workshop on WHO ATC/DDD Methodology and Drug Utilization Research; and the 38th Annual Meeting of Representatives of the National Pharmacovigilance Centres participating in the WHO Programme for International Drug Monitoring.

Contents

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Table of Contents

Regulatory Matters

Safety of medicines

Table of Contents

Aripiprazole

Risk of certain impulse control behaviours

Canada. Health Canada has updated the Canadian prescribing information for aripiprazole (Abilify®) to include a warning statement of risk of pathological gambling and uncontrollable sexual behaviours (hypersexuality).

Aripiprazole is an oral medication and is used to treat:

- manic-depressive illness (bipolar I disorder) in adults and adolescents of 13 years and older. This condition is characterised by periods of elevated moods (mania) and depression;
- schizophrenia in adults and adolescents of 15 years and older;
- depression in adults when used in combination with other drugs.

Health Canada conducted a safety review following the European Medicines Agency (EMA)'s warning (product label update) of the risk of pathological gambling and the inclusion of hypersexuality as an adverse effect.

At the time of the review, Health Canada received five reports of pathological gambling and/or hypersexuality, suspected of being linked with aripiprazole. Upon review of these cases, no conclusions could be made regarding what role, if any, the drug may have played due to limited information.

Among 14 of the 18 cases of pathological gambling, and 5 of 6 cases of hypersexuality linked to aripiprazole identified in the scientific and medical literature, the behaviours resolved or improved when the treatment with aripiprazole was stopped or the dosage was reduced.

Health Canada will continue to monitor adverse effect information involving aripiprazole to investigate potential harms.

Reference:
Summary Safety Review, Health Canada, 2 November 2015 (*www.hc-sc.gc.ca*)

Asunaprevir and daclatasvir

Risk of interstitial pneumonia

Japan. The Ministry of Health, Labour and Welfare (MHLW) and the Pharmaceuticals and Medical Devices Agency (PMDA) have announced the revision of the package insert for asunaprevir (Sunvepra®) and daclatasvir (Daklinza®) to include risk of interstitial pneumonia.

Asunaprevir and daclatasvir are co-administered for treatment of serogroup 1 (genotype 1) chronic hepatitis C or compensated cirrhosis type C.

The MHLW/PMDA stated that cases of interstitial pneumonia have been reported in patients treated with asunaprevir and daclatasvir in Japan.

The MHLW/PMDA recommended the addition of the following text to the subsection of the "Clinically significant adverse reaction" in the section of the "Adverse reaction" in the package insert.

Interstitial pneumonia: Interstitial pneumonia may occur. If cough, dyspnoea, pyrexia, abnormal chest sound (crepitations) etc. are observed, examinations including chest X-ray, chest CT scan, or serum marker test should be performed. If interstitial pneumonia is suspected, administration of this drug should be discontinued and appropriate measures should be adopted.

Reference:
Revision of Precautions, MHLW/PMDA, 20 October 2015 (*www.pmda.go.jp/english/*)

Azithromycin

Risk of drug reaction with eosinophilia and systemic symptoms (DRESS)

Singapore. The Health Sciences Authority (HSA) has informed health-care professionals of the risk of eosinophilia and systemic symptoms (DRESS) associated with the use of azithromycin.

Azithromycin (Zithromax®) is a macrolide antibiotic (azalide subclass) used to treat upper and lower respiratory tract infections and other infections sensitive to azithromycin.

In April 2014, Health Canada updated package inserts (PI) of azithromycin-containing products to include information on DRESS. This was based on a report of DRESS suspected to be associated with azithromycin in Canada, and a review of published literature.

To date, the HSA has not received any reports of DRESS associated with the use of azithromycin, but initiated a labelling update for azithromycin to warn of reports of DRESS.

The HSA has recommended health-care professionals to be vigilant to the signs and symptoms of DRESS in patients who are prescribed azithromycin. These may include rash, fever, lymphadenopathy, haematological abnormalities and multi-organ involvement. Early and prompt discontinuation of the offending drug is important to achieve the best outcome in patients with DRESS.

Reference:
Product Safety Alerts, HSA, 30 September 2015 (*http://www.hsa.gov.sg/*)

(See WHO Pharmaceuticals Newsletters No.5, 2015: Risk of drug-induced hypersensitivity syndrome in Japan and No.6, 2014: Drug Reaction/Rash with Eosinophilia and Systemic Symptoms (DRESS) in Canada)

Ceftriaxone

Risk of acute generalised exanthematous pustulosis

Japan. The MHLW and the PMDA have announced the revision of the package insert ceftriaxone to include risk of acute generalised exanthematous pustulosis.

Ceftriaxone is an antimicrobial used to treat infections such as: sepsis, pharyngitis/ laryngitis, tonsillitis, acute bronchitis, pneumonia, lung abscess and pyothorax by several strains.

The MHLW/PMDA stated that cases of acute generalised exanthematous pustulosis have been reported in patients treated with ceftriaxone sodium hydrate in Japan and in other countries. In addition, the company core datasheet (CCDS) has been updated.

Based on expert advice and available evidence, the MHLW/PMDA have recommended the addition of the "Acute generalised exanthematous pustulosis" to the section of the "Clinically significant adverse reaction" in the package insert.

Reference:
Revision of Precautions, MHLW/PMDA, 20 October 2015 (*www.pmda.go.jp/english/*)

Clopidogrel

Long-term treatment does not change risk of death

USA. A US Food and Drug Administration (FDA) review has determined that long-term use of the blood-thinning drug clopidogrel (Plavix®) does not increase or decrease overall risk of death in patients with, or at risk of heart disease. The FDA evaluation of the Dual Antiplatelet Therapy (DAPT) trial and several other clinical trials also does not suggest that clopidogrel increases the risk of cancer or death from cancer. The FDA has been working with the manufacturers of clopidogrel to update the label to reflect the results of the mortality meta-analysis.

Clopidogrel is an antiplatelet medicine used to prevent blood clots in patients who have had a heart attack, stroke, or problems with the circulation in the arms and legs. It works by helping to keep the platelets in the blood from sticking together and forming clots that can occur with certain medical conditions.

In order to investigate the increased risk of death and cancer-related death reported with clopidogrel in the DAPT trial, the FDA examined the results of the DAPT trial and other large, long-term clinical trials of clopidogrel with data available on rates of death, death from cancer, or cancer reported as an adverse event.

The FDA performed meta-analyses of other long-term clinical trials to assess the effects of clopidogrel on death rates from all causes. The results indicate that long-term (12 months or longer) dual antiplatelet therapy with clopidogrel and aspirin do not appear to change the overall risk of death when compared to short-term (6 months or less) clopidogrel and aspirin, or aspirin alone. Also, there was no apparent increase in the risks of cancer-related deaths or cancer-related adverse events with long-term treatment.

The FDA has recommended that health-care professionals should consider the benefits and risks of available antiplatelet medicines before starting treatment.

Reference:
Drug Safety Communication, US FDA, 6 November 2015 (*www.fda.gov*)

Codeine

Suspension of use

Ethiopia. The Ethiopian Food, Medicine and Healthcare Administration and Control Authority (FMHACA) has suspended the use of codeine for all patients due to the risk of death and life threatening adverse effects.

The suspension is based on the US FDA reports of children who developed serious adverse effects after taking codeine for pain relief after tonsillectomy and/or adenoidectomy. These children had evidence of an inherited ability to convert codeine into morphine very rapidly.

Codeine is converted to morphine in the cytochrome P450 2D6 (CYP2D6). Some people have genetic background that makes this enzyme more active. These "ultra-rapid metabolizers" are more likely to have higher blood level of morphine after taking codeine. A study showed that Ethiopians are one of "ultra-rapid metabolizers", therefore Ethiopians are more susceptible for inadvertent adverse effects of codeine.

Even though the standard treatment guideline sets codeine as an alternative medicine for pain management

and dry cough, the FMHACA has decided to suspend the use of codeine for all patients in Ethiopia considering the genetic background.

Reference:
Communication from FMHACA to WHO, 25 November 2015

(See WHO Pharmaceuticals Newsletters No.3 and 4, 2015, No.5 and 4, 2013 and No.5, 2012 for related information)

Dipeptidyl peptidase-4 (DPP-4) Inhibitors

Risk of severe joint pain

Egypt. Egyptian Pharmaceutical Vigilance Center (EPVC) recommends the addition of a warning label to products containing dipeptidyl peptidase-4 (DPP-4) inhibitors, to include Joint Pain (Arthralgia).

DPP-4 inhibitors (e.g. sitagliptin, saxagliptin, linagliptin, and alogliptin) combined with diet and exercise are used to lower blood sugar in adults with type 2 diabetes. These medicines are available as single-ingredient products and in combination with other diabetes medicines such as metformin.

This recommendation was based on the US FDA warning of severe and disabling joint pain associated with the use of DPP-4 inhibitors.

Reference:
Newsletter, EPVC, Volume 6, Issue 11, November 2015

(See WHO Pharmaceuticals Newsletter No.5, 2015: DPP-4 inhibitors for Type 2 diabetes may cause severe joint pain in the United States of America)

Dutasteride

Risk of hepatic function disorder and jaundice

Japan. The MHLW and the PMDA have announced the revision of the package insert for dutasteride (Avolve® and Zagallo®) to include risk of hepatic function disorder and jaundice.

Dutasteride is used for benign prostatic hyperplasia and male pattern hair loss (androgenetic alopecia).

The MHLW/PMDA stated that cases of hepatic function disorder and jaundice have been reported in patients treated with dutasteride in Japan.

Based on expert advice and available evidence, the MHLW/PMDA have recommended the addition of the following text to the subsection of the "Clinically significant adverse reaction" in the section of "Adverse reaction" in the package insert.

Hepatic function disorder, jaundice:
Hepatic function disorder or jaundice associated with increased levels of AST (GOT), ALT (GPT), bilirubin, etc. may occur. Patients should be carefully monitored. If any abnormalities are observed, appropriate measures such as discontinuation of administration should be adopted.

Reference:
Revision of Precautions, MHLW/PMDA, 20 October 2015 (*www.pmda.go.jp/english/*)

Galantamine

Risk of rhabdomyolysis

Japan. The MHLW and the PMDA have announced the revision of the package insert for galantamine (Reminyl®) to include risk of rhabdomyolysis.

Galantamine is used to suppress progression of dementia symptoms in patients with mild to moderate Alzheimer's type dementia.

The MHLW/PMDA stated that cases of rhabdomyolysis have been reported in patients treated with galantamine hydrobromide in Japan.

Based on expert advice and available evidence, the MHLW/PMDA have recommended the addition of the following text to the subsection of the "Clinically significant adverse reaction" in the section of the "Adverse reaction" in the package insert.

Rhabdomyolysis:
Rhabdomyolysis may occur. Patients should be carefully monitored. If symptoms including myalgia, feelings of weakness, increased creatine kinase (creatine phosphokinase), or increased blood and urine myoglobin are observed, administration of this drug should be discontinued and appropriate measures should be adopted.

Reference:
Revision of Precautions, MHLW/PMDA, 20 October 2015 (*www.pmda.go.jp/english/*)

Hepatitis C treatments (Viekira Pak® and Technivie®)

Risk of serious liver injury

USA. The US FDA has issued a warning that hepatitis C treatments, a fixed-dose combination of dasabuvir, ombitasvir, paritaprevir and ritonavir (Viekira Pak®) and a fixed-dose combination of ombitasvir, paritaprevir and ritonavir (Technivie®) can cause serious liver injury in patients with underlying advanced liver disease.

Cases of hepatic decompensation and liver failure in patients with underlying liver cirrhosis were identified in patients who were taking these medicines. Some of these events resulted in serious outcomes including, liver transplantation or death, mostly in patients taking Viekira Pak® with evidence of advanced cirrhosis even before starting treatment.

At least 26 worldwide cases submitted to FDA Adverse Event Reporting System were considered to be possibly or probably related to these medicines. Some of the cases occurred in patients for whom these medicines were contraindicated or not recommended.

The FDA requires manufacturers to include information about serious liver injury adverse events to the Contraindications, Warnings and Precautions, Postmarketing Experience and Hepatic Impairment sections of the Viekira Pak® and Technivie® labels.

Reference:
Drug Safety Communication, US FDA, 22 October 2015 (*www.fda.gov*)

Iodine-containing contrast agents for medical imaging

to see blood vessels and organs in medical images such as X-rays or computed tomography (CT) scans.

In all of the reported cases, the infants were either premature or had other serious underlying medical conditions. Based on available evidence the FDA believes that this rare occurrence is usually temporary and resolves without treatment or any lasting effects.

The FDA will continue to evaluate this issue. Manufacturers of ICM products are required to conduct a study to investigate this further.

The FDA has recommended that health-care professionals should continue to follow the label recommendations for ICM products and continue to use clinical judgment to determine if testing for underactive thyroid is necessary.

Reference:
Drug Safety Communication, US FDA, 17 November 2015 (*www.fda.gov*)

Magnesium oxide

Risk of hypermagnesaemia

Japan. The MHLW and the PMDA have requested the revision of the package insert for magnesium oxide and magnesium oxide-containing medicines to include risk of

"Geriatrics" to the section of the "Careful administration" and addition of precautions regarding hypermagnesaemia to the "Use of geriatrics" section in the package insert.

The MHLW/PMDA also recommended the addition of the following precaution to the section of the "Important precaution" in the package insert.

- Use of the product should be kept to a minimum.
- Patients should be instructed to seek medical attention if they experience any symptoms, such as vomiting, bradycardia, muscular weakness, and somnolence.

Reference:
Revision of Precautions, MHLW/PMDA, 20 October 2015 (*www.pmda.go.jp/english/*)

Mirabegron

Risk of severe hypertension, associated cerebrovascular and cardiac events

The United Kingdom. The Medicines and Healthcare Products Regulatory Agency (MHRA) has announced that mirabegron is now contraindicated in patients with severe uncontrolled hypertension (systolic blood pressure ≥180 mmHg or diastolic blood pressure ≥110 mmHg, or both). The MHRA