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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 specialized 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 provides signals based on information derived from Individual Case Safety Reports (ICSRs) available in the WHO Global ICSR database, VigiBase®.

As the Feature article, we have included a brief report from two recent WHO-led pharmacovigilance training events.

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Agomelatine

Risk of hepatic injury

Australia. The Therapeutic Goods Administration (TGA) has informed health professionals that the Product Information (PI) for agomelatine (Valdoxan®) has been updated to include further information about the risk of hepatic injury.

Agomelatine is a melatonin receptor (MT_1 and MT_2) agonist and 5-hydroxytryptamine (serotonin) receptor 2C antagonist. It is indicated for treatment of major depression in adults, including prevention of relapse.

The updated PI advises caution should be taken before initiation of treatment with agomelatine, and there should be close surveillance of liver function during continuation of treatment. This is important if agomelatine is used in combination with other medicines associated with risk of hepatic injury or where risk factors for hepatic injury, such as overweight/obesity, non-alcoholic fatty liver disease, diabetes and substantial alcohol consumption, are present.

In addition, liver function tests are recommended for all patients before initiation of treatment and/or after a dose increase. Tests should be repeated at week three, six, 12, 24 post initiation of treatment, after a dose increase and thereafter when clinically indicated.

Treatment should not be initiated if serum transaminase levels are greater than three times the upper limit of the normal range. If pre-treatment transaminase levels are greater than the upper limit of the normal range (but less than three times the upper limit), agomelatine should be used with caution.

Reference:
Medicines Safety Update, TGA, Vol. 6, No. 2, April 2015 (*www.tga.gov.au*)

(See WHO Pharmaceuticals Newsletters No.1, 2015 for risk of serious hepatic adverse reactions with agomelatine in Ireland, No.6, 2014 for risk of liver toxicity in Europe and No.6, 2012 for risk of dose-related hepatotoxicity and liver failure in the UK)

Amiodarone and hepatitis C treatments containing sofosbuvir

Serious slowing of the heart rate with co-administration

Egypt, EU and **USA.** The regulatory authorities have warned of serious symptomatic bradycardia when antiarrhythmic drug amiodarone is used with hepatitis C treatments containing sofosbuvir in combination with other drugs (e.g. ledipasvir, daclatasvir or simeprevir).

Sofosbuvir containing medicines (Harvoni® and Sovaldi®) are indicated for treatment of chronic hepatitis C virus, which can last a lifetime and lead to serious liver problems, including cirrhosis or liver cancer.

The US Food and Drug Administration (FDA) review of post-market reports of adverse events found that patients can develop serious and life-threatening symptomatic bradycardia when a sofosbuvir containing hepatitis C drug in combination with another direct-acting antiviral is taken together with amiodarone. The reports included the death of one patient due to cardiac arrest and three patients requiring placement of a pacemaker to regulate their heart rhythms. The other patients recovered after discontinuing either the hepatitis C drugs or amiodarone, or both. The cause of these events could not be determined. The FDA will continue to monitor sofosbuvir containing hepatitis C drugs for risks of serious symptomatic bradycardia and further investigate the reason why the use of amiodarone with these hepatitis C drugs led to the heart-related events.

The FDA recommends heart monitoring in an inpatient hospital setting for the first 48 hours. Subsequently, monitoring in a doctor's office or self-monitoring of the heart rate should be done every day through at least the first 2 weeks of treatment. Patients discontinuing amiodarone just prior to starting sofosbuvir containing hepatitis C drugs in combination with another direct-acting antiviral, should also undergo similar cardiac monitoring as outlined above.

The FDA is adding information about serious slowing of the heart rate, known as symptomatic bradycardia, to the labels of sofosbuvir containing hepatitis C drugs.

The Egyptian Pharmaceutical Vigilance Center (EPVC) has advised health-care professionals;

- A fixed dose combination with ledipasvir/sofosbuvir should not be co-administered with amiodarone.
- Sofosbuvir combined with another hepatitis C drug, such as investigational drug daclatasvir or simeprevir, should not be co-administered with amiodarone.
- Patients should be advised to seek medical attention immediately if they have signs and symptoms of symptomatic bradycardia including:

  - near-fainting or fainting (syncope)
  - dizziness or light headedness
  - malaise
  - weakness
  - excessive tiredness
  - shortness of breath
  - chest pains
  - confusion or memory problems
- For patients taking amiodarone who have no other alternative treatment options and who will be co-administered either a fixed dose combination with ledipasvir/sofosbuvir or sofosbuvir in combination with another direct acting antiviral:
  - counsel patients about the risk of serious symptomatic bradycardia
  - cardiac monitoring in an in-patient setting for the first 48 hours of co-administration is recommended, after which outpatient or self-monitoring of the heart rate would occur on a daily basis through at least the first 2 weeks of treatment
- Patients who are taking either a fixed dose combination with ledipasvir/sofosbuvir or sofosbuvir in combination with another direct acting antiviral, who need to start amiodarone therapy due to no other alternative treatment options, should undergo similar cardiac monitoring as outlined above.
- Due to the long half-life of amiodarone, patients discontinuing amiodarone just prior to starting a fixed dose combination with ledipasvir/sofosbuvir or sofosbuvir in combination with another direct-acting antiviral, should also undergo similar cardiac monitoring as outlined above.
- Encourage patients to read the patient information leaflet they receive with their prescription hepatitis C drugs and amiodarone as there may be new information.

Information in EU for health-care professionals include:

- Severe bradycardia and heart block have been reported in patients taking amiodarone and combination of sofosbuvir with ledipasvir, or amiodarone and a combination of sofosbuvir and daclatasvir. Of 8 cases reviewed up to April 2015, one case resulted in fatal cardiac arrest and two required pacemaker intervention.
- Onset of bradycardia was within 24 hours of initiating hepatitis C treatment in 6 cases and within 2 to 12 days in the other 2 cases. Rechallenge in the context of continued amiodarone treatment resulted in recurrence of symptomatic bradycardia in 2 cases. Recurrence was also seen on rechallenge with the antivirals 8 days after stopping amiodarone, but not 8 weeks after stopping.
- Amiodarone should only be initiated in patients treated with combination of sofosbuvir with ledipasvir, or sofosbuvir plus daclatasvir, if other antiarrhythmics are contra-indicated or not tolerated.
- If concomitant use with amiodarone is unavoidable, patients should be closely monitored, particularly during the first weeks of treatment. Those at high risk of bradyarrhythmia should be monitored in an appropriate clinical setting for 48 hours after starting concomitant treatment.
- Due to its long half-life, patients who have discontinued amiodarone within the past few months should also be monitored when starting hepatitis C treatment with combination of sofosbuvir with ledipasvir, or sofosbuvir plus daclatasvir.
- Patients receiving these hepatitis C medicines with amiodarone, with or without other medicines that lower heart rate, should be warned of the symptoms of bradycardia and heart block and should be advised to seek urgent medical advice if they experience them.
- The product information for these hepatitis C medicines will be updated appropriately. A letter will also be sent to health-care professionals involved in hepatitis C treatment explaining these risks and the measures to manage them.
- Because the number of patients taking amiodarone who have been exposed to combination of sofosbuvir with ledipasvir, or sofosbuvir plus daclatasvir is unknown, it is not possible to estimate the incidence of occurrence of these events. The mechanism behind the findings has not been established.

The regulatory authorities recommend that health-care professionals should not prescribe sofosbuvir containing hepatitis C drugs combined with another direct-acting antiviral drug with amiodarone. However, in cases where alternative treatment options are unavailable, patients should be closely monitored. As amiodarone persists for a long time in the body, monitoring is also needed if patients start such hepatitis C treatments within a few months of stopping amiodarone.

References:

Newsletter, Egyptian Pharmaceutical Vigilance Center (EPVC), Volume 6, Issue 5, May 2015

Press release, EMA, 24 April 2014 (*www.ema.europa.eu*)

Drug Safety Communication, US FDA, 24 March 2015 (*www.fda.gov*)

Amphetamines and methylphenidate

Risk of suicidal thoughts and behaviours

Canada. A safety review was initiated to evaluate information regarding the potential risk of suicidal related thoughts and behaviours with the use of amphetamine products or methylphenidate.

Amphetamine products (amphetamine, dextroamphetamine and lisdexamfetamine) and methylphenidate are used for the treatment of attention-deficit hyperactivity disorder (ADHD) in adults and children 6 years of age and older.

Cases of suicide related events have been reported with the use of amphetamine products or methylphenidate internationally. ADHD can be associated with other mental health conditions that may increase the risk of suicidal related thoughts and behaviours. Whilst most reports originating from Canada reported suicidal thoughts, a small number of suicide attempts and suicides were also reported. In general, the review of Canadian cases suggests that the use of amphetamine products or methylphenidate may contribute to suicidal related thoughts or actions in some patients with ADHD, either alone or in association with other mental conditions. At present, there is little information in the scientific literature to support this association.

A communication notifying the risk of suicide related thoughts and behaviours associated with amphetamine products and methylphenidate has been issued. Prescribing information for all amphetamine products and methylphenidate will be updated to include: reports of rare cases of suicidality in patients taking amphetamine products or methylphenidate. Although evidence is limited patients should be monitored for signs of suicidality.

Risks of suicide related thoughts and behaviours associated with the use of amphetamine products or methylphenidate will be continued to be monitored and evaluated.

Reference:
Summary Safety Review, Health Canada, 30 March 2015 (*www.hc-sc.gc.ca*)

Asunaprevir and daclatasvir hydrochloride

Risk of erythema multiforme

Japan. The Ministry of Health Labour and Welfare (MHLW) and the Pharmaceutical and Medical Devices Agency (PMDA) have announced the revision of the package insert for asunaprevir (Sunvepra®) and daclatasvir hydrochloride (Daklinza®) to include risk of erythema multiforme, following reports of cases occurring in Japan.

Asunaprevir and daclatasvir hydrochloride are indicated for treatment of viraemia in patients with serogroup 1 (genotype I) chronic hepatitis C or compensated cirrhosis type C.

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

Erythema multiforme: Erythema multiforme may occur. Patients should be carefully monitored. If any abnormalities are observed, administration of this drug should be discontinued and appropriate measures should be taken.

Reference:
Revision of Precautions, MHLW/PMDA, 23 April 2015 (*www.pmda.go.jp/english/*)

Azilsartan

Risk of "hepatic function disorder"

Japan. The MHLW and the PMDA have announced the revision of the package insert for azilsartan (Azilva®) to include risk of hepatic function disorder.

Azilsartan is indicated for hypertension.

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

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

Hepatic function disorder: Hepatic function disorder associated with elevated AST (GOT), ALT (GPT), and γ-GTP levels may occur. Patients should be carefully monitored. If any abnormalities are observed, administration of this drug should be discontinued and appropriate measures should be taken.

Reference:
Revision of Precautions,

MHLW/PMDA, 23 April 2015 (*www.pmda.go.jp/english/*)

BioCSL Fluvax®

Not for children under 5 years

Australia. The TGA has warned that health professionals should be reminded that bioCSL Fluvax® is registered for use in children from the age of 5 years and older, and must not be used in children under 5 years of age due to an increased risk of fever and febrile convulsions. The TGA also advises health professionals to avoid using Fluvax® as a generic term for influenza vaccine to minimise the potential for confusion.

The information is reinforced in the black box warning in the PI as follows:
WARNING: This season's vaccine is indicated for use only in persons aged 5 years and over. It must not be used in children under 5 years. It should only be used in children aged 5 to under 9 years based on careful consideration of potential risks and benefits in the individual.

Reference:
Medicines Safety Update, TGA, Vol. 6, No. 2, April 2015 (*www.tga.gov.au*)

Cefotaxime sodium is an antibacterial agent used for treatment of infections such as: sepsis, infective endocarditis, secondary infections secondary to trauma, thermal burn, surgical wound, acute bronchitis, pneumonia, and lung abscess.

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

Based on expert advice and available evidence, the MHLW/PMDA have recommended that: "acute generalised exanthematous pustulosis" should be added to the "Clinically significant adverse reactions" subsection of the "Adverse reactions" section in package insert.

Reference:
Revision of Precautions, MHLW/PMDA, 23 April 2015 (*www.pmda.go.jp/english/*)

Clopidogrel sulphate containing medicines

Risk of acute generalised exanthematous pustulosis

Japan. The MHLW and the PMDA have announced the revision of the package insert for clopidogrel sulphate

The MHLW/PMDA stated that cases of acute generalised exanthematous pustulosis have been reported in patients treated with clopidogrel sulphate in Japan and other countries, and the CCDS has been updated.

Based on expert advice and available evidence, the MHLW/PMDA have recommended that "acute generalised exanthematous pustulosis" should be added to the "Clinically significant adverse reactions" subsection of the "Adverse reactions" section in package insert.

Reference:
Revision of Precautions, MHLW/PMDA, 23 April 2015 (*www.pmda.go.jp/english/*)

Codeine-containing medicines

Not to be used in children below 12 years for cough and cold

EU. The EMA announced that the consensus of the Coordination Group for Mutual Recognition and Decentralised Procedures - Human (CMDh) are introducing new measures to minimise the risk of serious adverse effects (e.g. breathing problems), with codeine-containing medicines, when used for cough and cold in children. As a result of these new measures: