WHO PHARMACEUTICALS NEWSLETTER

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 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 from the Uppsala Monitoring Centre's SIGNAL document

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Regulatory Matters

Safety of Medicines

Signal

Azathioprine

Cytomegalovirus reactivation

Australia. The Therapeutic Goods administration (TGA) has warned about the risk of Cytomegalovirus reactivation associated with the use of Azathioprine**.**

Information about the risk of cytomegalovirus reactivation in patients with inflammatory bowel disease has been added to the Product Information for Azathioprine.

Azathioprine is used as an immunosuppressant antimetabolite. It can be used alone or in combination with corticosteroids and/or other immunosuppressive drugs and procedures.

The oral use of Azathioprine has been reported to be associated with Cytomegalovirus (CMV) which is a common viral infection that normally remains dormant until reactivated when T-lymphocyte mediated immunity is compromised. CMV viraemia can lead to secondary haemophagocytic syndrome.

TGA now advises that CMV viraemia resulting in severe pneumonitis and haemophagocytic syndrome in patients with inflammatory bowel disease has been reported in the literature. It recommends that caution be exercised and specialist literature consulted when assessing the risk of CMV reactivation and inflammatory bowel disease deterioration.

Four cases of CMV reactivation and/or haemophagocytic syndrome associated with azathioprine have been reported to the TGA since 1992.

Reference: Medicine Safety Update. June 2014. (www.tga.gov.au)

Docetaxel

Risk of alcohol intoxication

USA. The US Food and Drug Administration (FDA) is warning that the intravenous chemotherapy drug docetaxel contains ethanol, also known as alcohol, which may cause patients to experience intoxication or feel drunk during and after treatment. FDA is revising the labels of all docetaxel drug products to warn about this risk.

Docetaxel is a prescription chemotherapy drug used to treat different kinds of cancer, including cancers of the breast, prostate, stomach, head and neck cancers, and non-small-cell lung cancer.

Health-care professionals should consider the alcohol content of docetaxel when prescribing or administering the drug to patients, particularly in those whom alcohol intake should be avoided or minimized and when using it in conjunction with other medications.

Reference: FDA Safety Communications, US FDA, 20 June 2014. (www.fda.gov)

Etonogestrel/ethinyl estradiol slow release vaginal ring

New usage restrictions

Canada. Health Canada has endorsed important safety information on etonogestrel /ethinyl estradiol slow release vaginal ring (NUVARING®). New contraindications include the following:

- Etonogestrel /ethinyl estradiol should not be used by women who smoke (if over age 35), or who have severe or multpile risk factors for thrombosis, including: vulvular heart disease with complications, hypertension, severe dyslipoproteinemia, abnormality in proteins that regulate coagulation, diabetes mellitus with vascular involvement, or major surgery with prolonged immobilization.
- Etonogestrel /ethinyl estradiol should NOT be used by women who have experienced migraines with focal neurological symptoms, or pancreatitis associated with severe hypertriglyceridemia.
- Prescribers should consider the above new contraindications when discussing treatment options with their patients.

Reference: Health Canada, Important Safety Information, July 31, 2014. (www.canada.gc.ca)

Lidocaine Viscous

Should not be used to treat teething pain

USA. The US Food and Drug Administration (FDA) notified health professionals, their provider organizations and caregivers for infants, that prescription oral viscous lidocaine 2% solution should not be used to treat infants and children with teething pain. FDA is requiring a Boxed Warning to be added to the prescribing information (label) to highlight this information. Oral viscous lidocaine solution is not approved to treat teething pain, use in infants and young children can cause serious harm, including death.

Topical pain relievers and medications that are rubbed on the gums are not necessary or even useful because they wash out of the baby's mouth within minutes. When too much viscous lidocaine is given to infants and young children or they accidentally swallow too much, it can result in seizures, severe brain injury, and problems with the heart. Cases of overdose due to wrong

dosing or accidental ingestion have resulted in infants and children being hospitalized or dying.

In 2014, FDA reviewed 22 case reports of serious adverse reactions, including deaths, in infants and young children 5 months to 3.5 years of age who were given oral viscous lidocaine 2 percent solution for the treatment of mouth pain, including teething and stomatitis, or who had accidental ingestions.

Health care professionals should not prescribe or recommend this product for teething pain. Parents and caregivers should follow the American Academy of Pediatrics' recommendations for treating teething pain which includes the following:

- Use a teething ring chilled in the refrigerator (not frozen).
- Gently rub or massage the child's gums with your finger to relieve the symptoms.

FDA is also encouraging parents and caregivers not to use topical medications for teething pain that are available over the counter (OTC) because some of them can be harmful. FDA recommends following the American Academy of Pediatrics' recommendations to help lessen teething pain.

Reference: FDA Safety Communications, US FDA, 26 June 2014 (www.fda.gov).

Methadone (Oral)

Safety issues associated with high povidone content

Europe. The Coordination Group for Mutual Recognition and Decentralised Procedures – Human (CMDh) 1 has endorsed by consensus the recommendation to suspend the marketing authorisation of methadone oral (by mouth) solutions containing high molecular weight povidone. These products will remain suspended until they have been reformulated. Additionally, the CMDh agreed that methadone tablets that contain low molecular weight povidone should remain on the market with changes to the product information.

Methadone is used in rehabilitation programs to prevent or reduce withdrawal symptoms in patients dependent on opioids such as heroin. Some oral formulations of methadone also contain the additive povidone, which is available in different molecular weights. While these medicines are intended for oral use only, some patients may misuse oral methadone formulations by injecting them into a vein. If a medicine containing high molecular weight povidone (known as K90) is misused in this way, the povidone is not excreted from the body and accumulates inside the cells of vital organs, which may cause serious harm.

The safety of oral methadone medicines containing povidone was reviewed by the European Medicines Agency's (EMA) Pharmacovigilance Risk Assessment Committee (PRAC), following reports of serious adverse events in former or current drug abusers in Norway, which led to the suspension of methadone oral solutions containing povidone K90 from the Norwegian market.

The PRAC concluded that risk minimisation measures would be insufficient to mitigate the risks with oral solutions containing high molecular weight povidone, and therefore recommended that these products should be suspended. They will need to be appropriately reformulated before being reintroduced in the European market.

For methadone tablets containing povidone of lower molecular weight (e.g. K25 and K30), the available data showed that this kind of povidone is excreted from the body and does not accumulate inside the cells as high molecular weight povidone does. Therefore, these products will remain in the market and changes will be made to the product information (SmPC and package leaflet) to reinforce the message that tablets are for oral administration only and must not be taken in any other way.

As the PRAC recommendation was endorsed by consensus by the CMDh, it will now be implemented in all EU Member States where these medicines are marketed, according to an agreed timetable.

Reference*:* Press Release, EMA, 24 June 2014 (www.ema.europa.eu)

Ondansetron

New dosing restrictions

Canada. Health Canada has informed health-care professionals the new safety information regarding the dosage and administration of intravenous ondansetron in geriatrics (>65 years of age).

In geriatrics, ondansetron (Zofran ®) is indicated for the prevention of nausea and vomiting associated with emetogenic chemotherapy.

New dosing restrictions are recommended to mitigate the risk of QT prolongation in elderly patients (>65years of age).

The dosing restrictions for geriatrics are summarized below:

- In patients **≥75** years of age, the initial IV dose must not exceed **8mg**.

• In patients years of age, the initial IV dose must no exceed **16mg**.
• Subsequent IV doses must not exceed 8mg and may even be given 4 and 8 hours after the initial dose.
• All IV doses must be diluted in 50-100mL of saline or other compatible fluid.
• All IV doses must be infused over no less than 15 minutes.

There are no changes to the recommended oral dosing.

These recommendations follow a previous risk communication, which detailed that ondansetron caused dose-dependent prolongation of the QT interval, which can lead to the Torsade de Points, a potentially life-threatening heart arrhythmia. Caution must be used if administering the ondansetron to patients with risk factors for QT interval prolongation or cardiac arrhythmias and electrolyte imbalances should be corrected prior to ondansetron administration.

Reference: Health Canada, Important Safety Information. June 12, 2014. (www.canada.gc.ca)

Renin-Angiotensin system (RAS) acting agents

Restricted use, especially in diabetic nephropathy

Europe. The EMA's Committee for Medicinal Products for Human Use (CHMP) has endorsed restrictions on combining different classes of medicines that act on the renin-angiotensin system (RAS), a hormone system that controls blood pressure and the volume of fluids in the body.

These medicines (called RAS-acting agents) belong to three main classes: angiotensin-receptor blockers (ARBs, sometimes known as sartans), angiotensin-converting enzyme inhibitors (ACE-inhibitors) and direct renin inhibitors such as aliskiren. Combination of medicines from any two of these classes is not recommended and, in particular, patients with diabetes-related kidney problems (diabetic nephropathy) should not be given an ARB with an ACE-inhibitor.

Where combination of these medicines (dual blockade) is considered absolutely necessary, it must be carried out under specialist supervision with close monitoring of kidney function, fluid and salt balance and blood pressure. This would include the licensed use of the ARBs candesartan or valsartan as add-on therapy to ACE-inhibitors in patients with heart failure who require such a combination. The combination of aliskiren with an ARB or ACE-inhibitor is strictly contraindicated in those with kidney impairment or diabetes.

The CHMP opinion confirms recommendations made by the Agency's Pharmacovigilance Risk Assessment Committee (PRAC) in April 2014, following assessment of evidence from several large studies in patients with various pre-existing heart and circulatory disorders, or with type 2 diabetes. These studies found that combination of an ARB with an ACE-inhibitor was associated with an increased risk of hyperkalaemia (increased potassium in the blood), kidney damage or low blood pressure compared with using either medicine alone.

Reference: Press Release, EMA, 23 May 2014. (www.ema.europa.eu)

Serotonin Antagonists

Risk of seretonin syndrome

Canada. Health Canada has completed a safety review of the serotonin blocking drugs (serotonin antagonists): palonosetron, dolasetron, granisetron and ondansetron. These drugs are used for treating nausea and vomiting due to cancer therapy. This review identified a potential risk of serotonin syndrome occurring when serotonin accumulates to high levels in the body.

Health Canada has requested that manufacturers incorporate the risk of serotonin syndrome into the Warnings and Precautions section and the Consumer Information section of the Canadian Product Monograph for these drugs.

A 2012 signal in the World Health Organization (WHO) Pharmaceuticals Newsletter prompted the review. The publication indicated that ondansetron used together with other drugs that affect serotonin levels (serotonergic drugs) may contribute to the development of serotonin syndrome in susceptible patients.

Serotonin syndrome occurs when serotonin, a chemical normally found in the body, accumulates to high levels. This usually happens with combinations of certain drugs that affect serotonin levels, but may also occur with a single drug.

It is very important to diagnose serotonin syndrome early as it can be fatal if not treated. Symptoms of serotonin syndrome may include any combination of confusion, agitation, restlessness, muscle twitching or stiffness, fever, increased sweating and heart rate, blood pressure fluctuations, pupil

dilatation, nausea and/or vomiting, loss of consciousness and coma. Neuroleptic malignant syndrome is a life-threatening condition with changes in the nervous, muscular and cardiovascular system. Neuroleptic malignant syndrome is associated with the use of antipsychotics and dopamine enhancing drug and it presents with clinical features similar to serotonin syndrome. Dopamine is another chemical normally found in the body. The way neuroleptic malignant syndrome occurs in the body is different to how serotonin syndrome occurs in the body. However, these two syndromes raise a diagnostic problem to the healthcare professional. As the treating healthcare professional could misdiagnose serotonin syndrome, it is important that patients who experience any of these symptoms talk to a healthcare professional immediately.

Health Canada received two Canadian reports of serotonin syndrome with serotonin blocking drugs used to treat nausea and vomiting. One report described an incident of serotonin syndrome in a 30-year-old man taking ondansetron and other medications. The other report described an incident of serotonin syndrome and neuroleptic malignant syndrome in a 12-year-old boy taking granisetron and olanzapine. Both patients recovered

The Health Canada review noted that when used as indicated, serotonin blocking drugs used to treat nausea and vomiting alone are unlikely to cause serotonin syndrome. However, when these drugs are used in combination with other drugs that affect serotonin levels, the way they work together in the body could explain how serotonin syndrome can occur.

The Canadian Product Monographs for ALOXI®, KYTRIL®, and ZOFRAN® now contain this new safety information. ANZEMET® has recently been discontinued by the manufacturer in Canada. Manufacturers of generic versions of these drugs will also update their Product Monographs. On May 14, 2014 Health Canada also issued an Information Update to the public communicating the risk of serotonin syndrome with serotonin blocking drugs used to treat nausea and vomiting.

Reference: Advisories, Warnings and Recalls, Health Canada, May 14, 2014. (www.hc-sc.gc.ca)

Strontium ranelate

Cardiovascular and Skin Reactions reported

Saudi Arabia. The Saudi Food and Drug Authority (SFDA) advised health-care providers that strontium ranelate (Protelos®), which is indicated in treating severe osteoporosis in postmenopausal women, is no longer available in the Saudi market due to serious cardiovascular and skin adverse drug events.

This decision was based on a comprehensive review of the available evidence to assess the benefit/risk balance of using strontium ranelate in patients suffering from osteoporosis. This review involved a number of clinical trials, observational studies and post-marketing surveillance data for the product.

The evaluated data indicated that there is an increased risk of heart problems (such as myocardial infarction) among strontium ranelate users. Furthermore there were confirmed cases of serious skin and hypersensitivity reactions such as drug rash with eosinophilia and systemic symptoms (DRESS).

The aforementioned issue was discussed in the Saudi Pharmacovigilance Advisory Committee meeting and it was concluded that based on the available evidence, the risks associated with using strontium ranelate for osteoporosis outweigh potential benefits and the proposed risk minimization measures may not be sufficient to protect the patients. Therefore, the SFDA decided to revoke the marketing authorization of strontium ranelate from the local market due to aforementioned risks and the availability of safer alternatives.

Reference: Communication from National Pharmacovigilance and Drug Safety Centre, SFDA, 01 June 14 (www.sfda.gov.sa/npc)

Testosterone products

Risk of venous blood clots

USA. The US Food and Drug Administration (FDA) notified health professionals and their medical care organizations that it is requiring the manufacturers of all approved testosterone products to include a warning in the drug labelling about the risk of blood clots in the veins, also known as venous thromboembolism (VTE), including deep vein thrombosis (DVT) and pulmonary embolism (PE).

The risk of venous blood clots as a possible consequence of polycythaemia is already included in the labelling of testosterone products. Because there have been post market reports of venous blood clots unrelated to polycythaemia, FDA is requiring a change to drug labelling of all testosterone products to provide a more general warning regarding venous

blood clots, to ensure this risk is described consistently in the labelling of all approved testosterone products.
This new warning, a class labelling change, is not related to an ongoing FDA evaluation of the possible risk of stroke, heart attack, and death in patients taking testosterone products. FDA is currently evaluating the potential risk of these cardiovascular events, which are related to blood clots in the arteries.

Reference: FDA Safety Communications, US FDA, 20 June 2014 (www.fda.gov).