WHO PHARMACEUTICALS NEWSLETTER

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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 from the Uppsala Monitoring Centre's SIGNAL document.

This is the last issue of the newsletter in 2013. We thank you for your interest in this publication and wish you a very good year in 2014.

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Apixaban, dabigatran and rivaroxaban

Risk of serious haemorrhage—clarified contraindications apply to all three medicines

UK. The Medicines and Healthcare products Regulatory Agency (MHRA) announced that the contraindications for dabigatran (Pradaxa®) which include a range of conditions where the patient is at significant risk of major bleeding, also applied to the other two new oral anticoagulants apixaban (Eliquis®) and rivaroxaban (Xarelto®).

Dabigatran is a potent, orally active, direct inhibitor of free thrombin, fibrin-bound thrombin and thrombin-induced platelet aggregation. Apixaban and rivaroxaban are direct, highly selective, orally active inhibitors of activated factor X (factor Xa).

All three new oral anticoagulants are licensed for:

- prevention of venous thromboembolic events in adults who have had elective total hip-replacement or knee-replacement surgery
- prevention of stroke and systemic embolism in adults with non-valvular atrial fibrillation and one or more cardiovascular risk factors

Rivaroxaban is additionally licensed for:

- treatment of deep-vein thrombosis and pulmonary embolism, and prevention of their recurrence, in adults

The following contraindications now apply to all three new oral anticoagulants, dabigatran, apixaban and rivaroxaban, for all doses and indications:

- A lesion or condition, if considered a significant risk factor for major bleeding. This may include:
  - current or recent gastrointestinal ulceration
  - presence of malignant neoplasm at high risk of bleeding
  - recent brain or spinal injury
  - recent brain, spinal, or ophthalmic surgery
  - recent intracranial haemorrhage
  - known or suspected oesophageal varices
  - arteriovenous malformation
  - vascular aneurysms, or major intraspinal or intracerebral vascular abnormalities
- Concomitant treatment with any other anticoagulant agent—eg, unfractionated heparin, low molecular weight heparin (such as enoxaparin or dalteparin), heparin derivatives (such as fondaparinux), or oral anticoagulants (such as warfarin). Exceptions are switching of therapy to or from the medicine, or when unfractionated heparin is given at doses necessary to maintain an open central venous or arterial catheter

Additional advice and information for health-care professionals:

- Special care should be taken when deciding to prescribe these anticoagulant medicines to patients with other conditions, procedures, and concomitant treatments (eg, non-steroidal anti-inflammatory drugs, antiplatelets), which may increase the risk of major bleeding
- Attention should be paid to renal function. Impaired renal function may constitute a contraindication or recommendation not to use the anticoagulant medicine, or may require a dose reduction; recommendations differ for the three medicines
- The contraindications, posology, and warnings and precautions for use specific to each medicine, together with the individual's risk factors for bleeding (eg, renal function), should be considered before prescribing these medicines

It is also notified that there is no specific antidote available for any of these three new oral anticoagulants.

(See WHO Pharmaceuticals Newsletters Nos. 1 and 6, 2012 for safety review of post-market reports of serious bleeding events in the USA, Australia and New Zealand; Risk of serious haemorrhage, need for renal function testing in UK, and No.4, 2012 for modifications to product information for clearer guidance in EU).

Reference:
Drug Safety Update, October 2013, Volume 7, issue 3, A1 MHRA, (www.mhra.gov.uk).

Bevacizumab

Necrotising fasciitis

Australia. The Therapeutic Goods Administration (TGA) advised health professionals that the Product Information (PI) for bevacizumab (Avastin®) was updated to include a precaution about necrotising fasciitis. It is recommended that bevacizumab be discontinued and appropriate therapy

initiated promptly upon diagnosis.

Bevacizumab is an antineoplastic agent, a human monoclonal antibody that selectively binds and inhibits the biological activity of human vascular endothelial growth factor (VEGF). Inhibition of VEGF activity reduces the vascularisation of tumours, thereby hindering their growth.

Necrotising fasciitis is a life-threatening bacterial infection of the soft tissue. It is characterised by rapidly spreading necrosis of superficial fascia and subcutaneous tissue. Symptoms may include sudden severe pain in the affected area; redness, heat, swelling, or fluid-filled blisters in the skin; scaling, peeling, or discoloured skin over the affected area; and fever. Other symptoms may include confusion, fainting or dizziness.

Internationally, necrotising fasciitis has been reported in a small number of patients receiving bevacizumab in both clinical trials and in the postmarket setting. Some of these cases have been fatal. There have been no reports of necrotising fasciitis in patients receiving bevacizumab in Australia.

The reported cases show occurrence of necrotising fasciitis in patients with several different types of cancers. However, it has been found that the incidence of the infection associated with bevacizumab is rare and usually secondary to wound healing complications, gastrointestinal perforation or fistula formation.

(See WHO Pharmaceuticals Newsletter No.3, 2013 for Cases of necrotizing fasciitis in Canada)

Reference:
Medicines Safety Update Vol 4, No. 4, August 2013 (www.tga.gov.au).

Combined hormonal contraceptives

Benefits continue to outweigh risks

Europe. The European Medicines Agency completed its review of combined hormonal contraceptives (CHCs), particularly of the risk of venous thromboembolism (VTE) associated with their use. The European Medicines Agency's Committee for Medicinal Products for Human Use (CHMP) concluded that the benefits of CHCs in preventing unwanted pregnancies continue to outweigh their risks, and that the known risk of VTE with all low-dose CHCs (ethinylestradiol < 50 mcg) is small. Differences exist between CHCs in their risk of VTE depending on the type of progestogen they contain. Currently available data indicate that CHCs containing the progestogens levonorgestrel, norethisterone or norgestimate have the lowest risk of VTE.

The review also looked at the risk of arterial thromboembolism (ATE). This risk is very low and there is no evidence for a difference in the level of risk between products depending on the type of progestogen.

The review reinforced the importance of ensuring that clear and up-to-date information is provided to women who use these medicines and to the healthcare professionals giving advice and clinical care.

The product information of CHCs will be updated to help women make informed decisions about their choice of contraception together with their healthcare professional. It is important that women are made aware of the risk of VTE and its signs and symptoms, and that doctors take into consideration a woman's individual risk factors when prescribing a contraceptive. Doctors should also consider how the risk of VTE with a particular CHC compares with other CHCs.

The CHMP opinion, in agreement with the previous recommendation by the Pharmacovigilance Risk Assessment Committee (PRAC), will now be sent to the European Commission for the adoption of a legally binding decision to update the product information of all CHCs throughout the EU.

Health-care professionals are also advised that:

- When prescribing a CHC, careful consideration should be given to the individual woman's current risk factors, particularly those for VTE, and the difference in risk of VTE between products. CHCs are contraindicated if a woman has one serious or multiple risk factors that put her at high risk of blood clots.
- Because a woman's individual risk factors will change over time, there is a need to regularly re-assess the suitability of her contraceptive. It is also important to raise awareness of the signs and symptoms of VTE and ATE when prescribing a CHC.
- Health-care professionals should always consider the possibility of a CHC-associated thromboembolism when presented with a woman who has symptoms.

(See WHO Pharmaceuticals Newsletter No.2, 2013 for review of Diane 35 and other medicines started following the decision by the French medicines regulatory agency to suspend the drug in EU and Canada and No.4, 2013 for benefits of Diane 35 and its

generics outweigh risks in certain patient groups in EU).

Reference:
Press release, EMA, 22 November 2013 (*www.ema.europa.eu*).

Dexmedetomidine hydrochloride

Risk of cardiovascular events

Australia. The TGA reminded health professionals that careful patient selection and consideration of the setting in which dexmedetomidine hydrochloride (Precedex®) is used are crucial to ensuring its safe use and that it should only be used for the approved indications and should be administered in accordance with the instructions in the PI. It is also reminded that a controlled infusion device should be used for the administration of dexmedetomidine, and the dose and rate of infusion should not exceed that recommended in the PI.

Particular caution is required in the following situations:

- patients with hypovolaemia, as dexmedetomidine decreases sympathetic nervous system activity
- patients with some level of autonomic system dysfunction, such as those with diabetes and the elderly
- patients of all ages with high vagal tone
- with concomitant use of vasodilators, negatively chronotropic agents, and/or other agents with alpha2-adrenoceptor agonist activity, such as clonidine and droperidol.

Dexmedetomidine is a relatively selective alpha2-adrenoceptor agonist used for sedation. In an intensive care setting, dexmedetomidine is indicated for sedation of initially intubated patients. However, use of the drug by continuous infusion should not exceed 24 hours. Dexmedetomidine is also indicated for procedural sedation. It can be used for non-intubated patients before and/or during surgeries and other procedures.

Atrial fibrillation, bradycardia and hypotension are all listed as adverse effects or precautions in the current PI for dexmedetomidine. There is a warning in the Precautions section regarding use in the elderly, in patients with high vagal tone, or chronic diseases, such as diabetes and heart failure, and with concomitant drugs with a similar pharmacological action. In the past 10 years, the TGA has received a small number of spontaneous reports of cardiovascular events involving dexmedetomidine (of a kind listed as known adverse events in the PI).

Reference:
Medicines Safety Update Vol 4, No. 4, August 2013 (www.tga.gov.au).

Ezogabine

Linked to retinal abnormalities and blue skin discoloration

USA. The U.S. Food and Drug Administration (FDA) warned the public that ezogabine (Potiga®) can cause blue skin discoloration and eye abnormalities characterized by pigment changes in the retina. The US FDA does not currently know if these changes are reversible. The US FDA approved changes to the drug label, underscoring risks of abnormalities to the retina in the eye, potential vision loss, and skin discoloration, all of which may become permanent. The revised label includes a new boxed warning, because of the risk of abnormalities to the retina. It is advised that ezogabine use be limited to patients who have not responded adequately to several alternative therapies to decrease the frequency of seizures, or epilepsy, and for whom the benefits of treatment outweigh the risks.

Ezogabine is approved as adjunctive treatment of partial-onset seizures in adult patients 18 years and older. Pigment changes in the retina have the potential to cause serious eye disease with loss of vision. It is not yet known whether the retinal pigment changes caused by ezogabine lead to visual impairment, although several patients have been reported to have impaired visual acuity. In some cases, retinal abnormalities have been observed in the absence of skin discoloration. The skin discoloration in the reported cases appeared as blue pigmentation, predominantly on or around the lips or in the nail beds of the fingers or toes, but more widespread involvement of the face and legs has also been reported. Scleral and conjunctival discoloration, on the white of the eye and inside eyelids, has been observed as well. The skin discoloration generally occurred after four years of treatment with ezogabine, but has appeared sooner in some patients.

In light of this new safety information all patients taking ezogabine should have a baseline eye exam and periodic eye exams that should include visual acuity testing and dilated fundus photography, and may include fluorescein angiograms (FA), ocular coherence tomography (OCT), perimetry, and electroretinograms (ERG). Ezogabine should be discontinued if ophthalmic changes are observed unless no other treatment options are available. If a patient develops skin discoloration, serious

consideration should be given to changing to an alternate medication. Patients who are taking ezogabine and develop any changes in their vision or any discoloration of their skin, including of their lips and nail beds, should contact their health care professional right away.

Patients should not stop taking ezogabine without talking to their health-care professional. Stopping such treatment suddenly can cause serious and life-threatening medical problems such as recurrence of seizures.

(See WHO Pharmaceuticals Newsletter NO.3, 2013 for link to retinal abnormalities and blue skin discoloration in the USA).

References:
FDA Drug Safety Communication, US FDA 1 November 2013 (*www.fda.gov*).

Fentanyl patches

Packaging changes to minimize risk of accidental exposure

USA. The US FDA required colour changes to the writing on fentanyl (Duragesic® and generics) pain patches so they can be seen more easily. The US FDA continues to learn of deaths from accidental exposure to fentanyl patches. Fentanyl patch is a strong prescription pain medicine that contains a narcotic opioid.

Patients and health-care professionals are reminded that fentanyl patches are dangerous even after they've been used because they still contain high amounts of strong narcotic pain medicine. Accidental exposure to these patches can cause serious harm and death in children, pets, and others.

In an effort to minimize the risk of accidental exposure to fentanyl patches, the US FDA is requiring the manufacturer of fentanyl to print the name and strength of the drug on the patch in long-lasting ink, in a colour that is clearly visible to patients and caregivers. The current ink colour varies by strength and is not always easy to see. This change is intended to enable patients and caregivers to more easily find patches on patients' bodies and see patches that have fallen off, which children or pets could accidentally touch or ingest. The manufacturers of generic fentanyl patches are being requested to make similar changes.

Patients are recommended to be aware that patches that are not stuck to the skin tightly enough may accidentally fall off a patient and stick to someone in close contact, such as a child. Used fentanyl patches require proper disposal after use — fold the patch, sticky sides together, and flush it down the toilet right away.

(See WHO Pharmaceuticals Newsletter No.2, 2009 for Warning about accidental child exposure and No.4, 2005 for labelling update in Canada)

References:
FDA Drug Safety Communication, US FDA 23 September 2013 (*www.fda.gov*).

Low Molecular Weight Heparins

Recommendations to decrease risk of spinal column bleeding and paralysis

USA. The US FDA recommended that health-care professionals carefully consider the timing of spinal catheter placement and removal in patients taking anticoagulant drugs, such as enoxaparin, and delay dosing of anticoagulant medications for some time interval after catheter removal to decrease the risk of spinal column bleeding and subsequent paralysis after spinal injections, including epidural procedures and lumbar punctures. These new timing recommendations, which can decrease the risk of epidural or spinal hematoma, will be added to the labels of anticoagulant drugs known as low molecular weight heparins, including Lovenox® and generic enoxaparin products and similar products.

Epidural or spinal hematomas are a known risk of enoxaparin in the setting of spinal procedures and are already described in the Boxed Warning and the Warnings and Precautions sections of the labels for Lovenox® and generic enoxaparin products. However, these serious adverse events continue to occur. To address this safety concern, the US FDA worked with the manufacturer of Lovenox®, Sanofi-Aventis, to further evaluate this risk and to update the Warnings and Precautions section of the Lovenox label with these additional timing recommendations. The labels for generic enoxaparin products will also be revised accordingly, as will those of other low molecular weight heparin-type products.

It is important to note that all anticoagulants carry the risk of causing spinal bleeding when used in conjunction with epidural/spinal anaesthesia or spinal puncture. The US FDA is continuing to evaluate the safety of other anticoagulants to determine if additional label changes are needed.

References:
FDA Drug Safety Communication, US FDA 6 November 2013 (*www.fda.gov*).

Mefloquine

Strengthened warnings on neuropsychiatric side effects

UK. The MHRA announced that, although the risk of neuropsychiatric side effects with mefloquine is well-established, a recent review of the prescribing information has led to strengthened warnings and new measures to help minimise risks. The overall safety profile of the drug has also been clarified in the product information.

Mefloquine (Lariam®) is used for prophylaxis and treatment of *Plasmodium falciparum* malaria. Official guidance on the appropriate use of antimalarial medicines and the prevalence of resistance should be considered when prescribing mefloquine .

Updated information and advice for health-care professionals:

- Psychiatric symptoms associated with use of mefloquine such as nightmares, acute anxiety, depression, restlessness, or confusion should be regarded as potentially prodromal for a more serious event
- Cases of suicide, suicidal thoughts, and self-endangering behaviour such as attempted suicide have been reported in association
- To minimise the risk of these adverse reactions, mefloquine must not be used for chemoprophylaxis in patients with active or a history of psychiatric disturbances such as depression, anxiety disorders, schizophrenia, or other psychiatric disorders
- If neuropsychiatric reactions or changes to mental state occur during mefloquine chemoprophylaxis, the patient should be advised to stop taking mefloquine and seek medical advice as soon as possible so that it can be replaced by another medicine for malaria prevention

It is also notified that the Marketing Authorisation Holder is issuing a letter to health-care professionals, a prescriber checklist, and patient alert card to aid compliance with these warnings, and to ensure patients are more aware of the neuropsychiatric side effects and to react promptly when these occur in malaria chemoprophylaxis.

(See WHO Pharmaceuticals Newsletter NO.5, 2013 for risk of serious psychiatric and nerve side effects in the USA)

Reference:

Drug Safety Update, November 2013, Volume 7, issue 4, A5 MHRA, (*www.mhra.gov.uk*).

risk of reactivation of hepatitis B virus (HBV) infection. The revised labels also include additional recommendations for screening, monitoring, and managing patients on these drugs to decrease this risk.

In patients with prior HBV infection, HBV reactivation may occur when the body's immune system is impaired. HBV reactivation has occurred in patients with prior HBV exposure who are later treated with drugs classified as CD20-directed cytolytic antibodies, including ofatumumab and rituximab. Some cases have resulted in fulminant hepatitis, hepatic failure, and death.

Ofatumumab is used to treat chronic lymphocytic leukemia (CLL) in patients who have further disease after treatment with the anti-cancer drugs fludarabine and alemtuzumab. Rituxan is used to treat non-Hodgkin's lymphoma and CLL. It is also used to treat other medical conditions, including rheumatoid arthritis, granulomatosis with polyangiitis, and microscopic polyangiitis.

To decrease the risk of HBV reactivation, the US FDA recommended that health-care professionals:

- Screen all patients for HBV infection before starting treatment with ofatumumab or rituximab by measuring hepatitis B surface antigen (HBsAg) and hepatitis B core antibody (anti-HBc).