WHO PHARMACEUTICALS NEWSLETTER

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WHO Collaborating Centre for
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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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This Newsletter is also available on our Internet website:
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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

The feature article in this issue gives you an overview of the WHO programme for the monitoring and surveillance of Substandard, Spurious, Falsely labelled, Falsified and Counterfeit (SSFFC) medical products.

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Belimumab

Progressive Multifocal Leukoencephalopathy (PML) reported in patients

Canada. GlaxoSmithKline, in consultation with Health Canada, informed health-care professionals of important new safety information regarding Progressive Multifocal Leukoencephalopathy (PML) reported in patients receiving belimumab (Benlysta™)). Belimumab is indicated, in addition to standard therapy, for reducing disease activity in adult patients with active, autoantibody-positive, systemic lupus erythematosus (SLE).

Two cases of PML have been reported spontaneously in adult female patients receiving belimumab out of an estimated post-marketing exposure of over 15,000 SLE patient exposures. Both patients were also receiving mycophenolate mofetil (MMF) and prednisone. One of the patients died.

Health-care providers should consider a diagnosis of PML in any patient on belimumab, presenting with new onset deficits or deterioration in cognition, speech or ocular functions, and/or motor and gait disturbances. Seizures may also occur.

If PML is suspected, the patient should be urgently referred to a neurologist, or other appropriate specialist. Where appropriate, treatment with belimumab and other immunosuppressant therapy should be withheld until PML is excluded.

Reference : Advisories, Warnings and Recalls, Health Canada, 22 April 2014 (www.hc-sc.gc.ca).

Caustinerf arsenical and yranicid arsenical

Recommendation to revoke authorisations of use of caustinerf arsenical and yranicid arsenical in dental procedure

Europe. The European Medicines Agency's (EMA) Committee for Medicinal Products for Human Use (CHMP) has recommended that the marketing authorisations for the dental pastes caustinerf arsenical, yranicid arsenical and associated names be revoked in the EU due to concerns over the risk of genotoxic effects and cell death in tissues around the teeth. The dental pastes, which contain an arsenic-based compound, arsenic trioxide, have been used to remove the damaged nerves in the dental pulp (the inside of the tooth).

In a review of the benefits and risks of these dental products, analyses of data from laboratory and population studies indicate that the arsenic contained in them may pose a risk of genotoxic effects that could increase the risk of cancer. In addition, there have been a small number of cases where arsenic is thought to have leaked into the areas around the teeth, causing parts of the tissue to die, including bone (osteonecrosis).

Post-marketing surveillance of caustinerf arsenical and yranicid arsenical has identified a small number of cases of periodontal necrosis, including 12 cases of osteonecrosis. The majority of cases occurred within 7 days of using the pastes.

During the review, the CHMP considered measures to minimize the risks identified with these products but concluded that restrictions and additional guidance to dentists would not reduce the risks to an acceptable level.

The EMA has concluded that the benefits of caustinerf arsenical, yranicid arsenical and associated products do not outweigh their risks and has recommended that their marketing authorisations in the EU be revoked. Dentists should use other alternative methods available for removing dental pulp.

Reference: Press Release, EMA, 08 May 2014 (www.ema.europa.eu).

Cyclizine

Restricted use in children under 6 years of age

Egypt. Egyptian Pharmaceutical Vigilance Center (EPVC) has recommended that cyclizine use in children under six years of age should be restricted. Marketing authorization holders of products containing cyclizine should update the product label to include restrictions of use in children under six years.

Cyclizine is a piperazine derivative with histamine H1-receptor antagonist activity and is indicated in motion sickness. The precise mechanism of action is not well understood. It may have effects directly on the labyrinthine apparatus and on the chemoreceptor trigger zone. Cyclizine exerts a central anticholinergic (anti-muscarinic) action.

Recommendations for Health-care Professionals (HCPs)

1. **Cyclizine dose by mouth or by intravenous injection over 3-5 minutes**: Child 6-12 years 25 mg up to 3 times daily and Child 12-18 years 50 mg up to 3 times daily.

2. **Cyclizine dose by rectum**: Child 6-12 years 25 mg up to 3 times daily and Child 12-18

years 50 mg up to 3 times daily.

3. **Cyclizine dose by continuous intravenous or sub-cutaneous infusion**: Child 6-12 years 75 mg over 24 hours and Child 12-18 years 150 mg over 24 hours.

***References*:** Egyptian Pharmaceutical Vigilance Center (EPVC), Newsletter. May 2014, Volume 5, Issue 5.

Dabigatran

Risks as compared to warfarin

USA. The U.S Food and Drug Administration (FDA) recently completed a new study comparing patients on dabigatran (Pradaxa®) to warfarin, for risk of ischaemic or clot-related stroke, bleeding in the brain, major gastrointestinal (GI) bleeding, myocardial infarction (MI), and death. The new study included information from more than 134,000 patients, 65 years or older, and found that among new users of blood-thinning drugs, dabigatran was associated with a lower risk of clot-related strokes, bleeding in the brain, and death, than warfarin. The study also found an increased risk of major gastrointestinal bleeding with use of dabigatran as compared to warfarin. The MI risk was similar for the two drugs.

Importantly, the new study is based on a much larger and older patient population than those used in FDA's earlier review of post-market data, and employed a more sophisticated analytical method to capture and analyse the events of concern. This study's findings, except with regard to MI, are consistent with the clinical trial results that provided the basis for dabigatran's approval. As a result of these latest findings, the FDA still considers dabigatran to have a favourable benefit to risk profile and have made no changes to the current label or recommendations for use.

Patients should not stop taking dabigatran (or warfarin) without first talking with their health-care professionals. Stopping the use of blood-thinning medications such as dabigatran and warfarin can increase the risk of stroke and lead to permanent disability and death. Health-care professionals who prescribe dabigatran should continue to follow the dosing recommendations in the drug label.

References: FDA Safety Communication, US FDA, 13 May 2014 (www.fda.gov).

Epidural corticosteroid injection

Risk of rare but serious neurologic problems

USA. The FDA is warning that injection of corticosteroids (including methylprednisolone, hydrocortisone, triamcinolone, betamethasone, dexamethasone) into the epidural space of the spine may result in rare but serious adverse events, including loss of vision, stroke, paralysis, and death. The injections are given to treat neck and back pain, and radiating pain in the arms and legs. The effectiveness and safety of epidural administration of corticosteroids have not been established, and FDA has not approved corticosteroids for this use.

FDA is requiring the addition of a Warning to the drug labels of injectable corticosteroids to describe these risks.

FDA will convene an Advisory Committee meeting of external experts in late 2014 to discuss the benefits and risks of epidural corticosteroid injections and to determine if further FDA actions are needed.

References: FDA Safety Communication, US FDA, 23 April 2014 (www.fda.gov).

Eszopiclone containing sleep aids

Can cause next-day impairment

USA. The FDA has notified health professionals and their medical care organizations of a new warning that the insomnia drug eszopiclone (Lunesta®) can cause next-day impairment of driving and other activities that require alertness. FDA recommends a decreased starting dose of eszopiclone to 1 mg at bedtime. Women and men are equally susceptible to impairment from eszopiclone, so the recommended starting dose of 1 mg is the same for both. FDA approved changes to the eszopiclone (Lunesta®) prescribing information and the patient Medication Guide to include these new recommendations. The drug labels for generic eszopiclone products will also be updated to include these changes.

A study of eszopiclone found that the previously recommended dose of 3 mg can cause impairment to driving skills, memory, and coordination that can last more than 11 hours after receiving an evening dose. Despite these driving and other problems, patients were often unaware they were impaired. The new lower recommended starting dose of 1 mg at bedtime will result in less drug in the blood the next day.

References: FDA Safety Communication, US FDA, 15 May 2014 (www.fda.gov).

Filgrastim and pegfilgrastim

Risk of Capillary Leak Syndrome (CLS)

Canada. Amgen Canada Inc., in consultation with Health Canada, informed health-care professionals of the risk of Capillary Leak Syndrome (CLS) associated with the granulocyte colony stimulating factors (G-CSF) filgrastim and pegfilgrastim.

Filgrastim (Neupogen®) is associated with a risk of CLS in patients with cancer and in healthy donors. Pegfilgrastim (Neulasta®) is associated with a risk of CLS in patients with cancer.

Cases of CLS have been reported in:

a. patients undergoing chemotherapy who were receiving filgrastim or pegfilgrastim and

b. donors undergoing peripheral blood progenitor cell mobilization who were receiving filgrastim.

CLS can cause circulatory shock and may be fatal. It is associated with hypotension, generalized edema, hypoalbuminemia and hemoconcentration. Episodes can vary in frequency and severity. Should symptoms of CLS be suspected, administration of filgrastim or pegfilgrastim should be stopped and the patient closely monitored. The Product Monographs (Neupogen® and Neulasta®) are being updated to reflect this new safety information.

Filgrastim is indicated to: decrease the incidence of infection, as manifested by febrile neutropenia, in patients with non-myeloid malignancies receiving myelosuppressive anti-neoplastic drugs, and for the prevention and treatment of neutropenia, to maintain a normal Absolute Neutrophil Count (ANC) in bone marrow transplant patients and in patients with HIV infection.

Pegfilgrastim is indicated to:

decrease the incidence of infection, as manifested by febrile neutropenia, in patients with non-myeloid malignancies receiving myelosuppressive anti-neoplastic drugs.

Reference : Advisories, Warnings and Recalls, Health Canada, 10 April 2014 (www.hc-sc.gc.ca).

Mirtazapine

Association with QT prolongation/*Torsades de Pointes*

Canada. Merck Canada Inc., in consultation with Health Canada, informed health-care professionals of important new recommendations for mirtazapine (Remeron® / REMERON RD®) regarding post-marketing cases of QT prolongation and *torsades de pointes* with the use of mirtazapine (REMERON® / REMERON RD®) . Most cases occurred in association with drug overdose or in patients with other risk factors for QT prolongation, including concomitant use of QT prolonging medications.

The Product Monograph has been updated to include this information and to advise caution in patients with risk factors such as known cardiovascular disease, family history of QT prolongation and concomitant use of QT prolonging medications. Monitoring of vital signs and cardiac rhythm should be undertaken in the management of mirtazapine overdose.

Serious outcomes including *torsades de pointes* and death have been reported with mirtazapine overdose. Patients with *torsades de pointes* may present with dizziness, palpitations, syncope, or seizures. If sustained, *torsades de pointes* can progress to ventricular fibrillation and sudden cardiac death.

Mirtazapine is indicated for the symptomatic relief of depressive illness.

References: Advisories, Warnings and Recalls, Health Canada, 28 March 2014 (www.hc-sc.gc.ca).

Meclizine

Restriction of use

Egypt. Based on the Egyptian Pharmaceutical Vigilance Centre (EPVC) assessment study, the Pharmacovigilance Committee recommends:

1. Not to use meclizine in children under two years of age.
2. Allowing the usage under medical supervision only in children from 2-12 years of age.
3. The product label should state this recommendation clearly.

Meclizine is a first-generation antihistamine of the piperazine class. It is structurally and pharmacologically similar to buclizine, cyclizine, and hydroxyzine, but has a shorter half-life of six hours compared to cyclizine and hydroxyzine with about 20 hours.

***References*:** Egyptian Pharmaceutical Vigilance Centre (EPVC) Newsletter, May 2014, Volume 5, Issue 5.

Temozolomide

Risk of hepatic injury

Canada. Merck Canada Inc., in consultation with Health Canada, informed health-care professionals of new warnings for temozolomide (TEMODAL®) regarding cases of hepatic injury, including

fatal hepatic failure reported post-marketing.

Temozolomide is an antineoplastic agent indicated for the treatment of adult patients with newly diagnosed glioblastoma multiforme concomitantly with radiotherapy and then as maintenance treatment. It is also indicated for treatment of adult patients with glioblastoma multiforme or anaplastic astrocytoma and documented evidence of recurrence or progression after standard therapy.

Cases of hepatic injury, including fatal hepatic failure, have been reported in patients receiving temozolomide. Liver toxicity may occur several weeks after initiation of treatment or after temozolomide discontinuation.

Liver function tests should be performed

- prior to treatment initiation;
- after each treatment cycle;
- midway during the treatment cycle for patients on a 42 day treatment cycle.

For patients with significant liver function abnormalities, the benefits and risks of continuing treatment should be carefully considered.

In total, 44 cases of hepatic injury, including fatal hepatic failure (19 cases) were identified in patients receiving temozolomide from market introduction (19 January 1994) through 15 March 2013.

The temozolomide (Temodal®) product monograph has been revised to include updated information on the risk of hepatic injury and specific recommendations for monitoring of liver function.

Reference : Advisories, Warnings and Recalls, Health Canada, 07 May 2014 (www.hc-sc.gc.ca).

Vemurafenib

Association of vemurafenib use with Drug Induced Liver Injury (DILI)

Canada. Hoffmann-La Roche Limited (Roche Canada), in consultation with Health Canada, informed health-care professionals of important new safety information regarding the risk of Drug Induced Liver Injury (DILI) reported with vemurafenib (Zelboraf®).

Vemurafenib is indicated as a monotherapy for the treatment of BRAF V600 mutation-positive unresectable or metastatic melanoma.

DILI, including cases of severe liver injury, has been reported with vemurafenib.

As of September 26, 2013, 63 cases out of an estimated 20,000 patients treated with vemurafenib (Zelforab®) were identified as having experienced DILI.

There were no reported deaths among the 63 cases of liver injury. There were two severe cases, both reported as hepatic failure; the outcome of one case of severe liver injury was reported as completely resolved with vemurafenib discontinuation while the outcome of the second severe liver injury case is not available at this time.

The Product Monograph (Zelboraf®) will be updated to include appropriate information regarding the risk of DILI and physicians should discuss the currently available information regarding benefits and risks of vemurafenib with their patients.

Prescribers are reminded to monitor transaminases, alkaline phosphatase, and bilirubin before initiation of vemurafenib treatment and monthly during treatment, or as clinically indicated. Liver injury should be managed using dose reduction, temporary interruption, or treatment discontinuation of vemurafenib.

Reference : Advisories, Warnings and Recalls, Health Canada, 7 April 2014 (www.hc-sc.gc.ca).

Hydroxyzine-containing medicines

Review started

Europe. The European Medicines Agency (EMA) has started a review of hydroxyzine-containing medicines, which have been approved in most EU countries for a variety of uses including anxiety disorders, as premedication before surgery, for relief of pruritus (itching), and for sleep disorders.

The review was requested by the Hungarian medicines agency (GYEMSZI-OGYI) over concerns about the side effects of these medicines on the heart. This followed an examination of the benefits and risks by a marketing authorisation holder for hydroxyzine. Data from drug safety monitoring (pharmacovigilance) and published experimental studies identified a potentially increased risk of alterations of the electrical activity of the heart and arrhythmias (irregular heartbeats). As hydroxyzine-containing medicines are approved in other EU countries, the Hungarian agency decided to trigger an EU-wide review.

The EMA will now review the available data on the benefits and risks of hydroxyzine-containing medicines in all authorized indications, and issue an opinion on the

Ivabradine

Review started

Europe. The EMA has started a review of the medicine ivabradine (Corlentor/Procoralan®). Ivabradine is used to treat the symptoms of adults with long term stable angina (chest pain due to obstruction in the arteries in the heart) or long term heart failure (when the heart cannot pump enough blood to the rest of the body). The review follows preliminary results from the SIGNIFY study, which was evaluating whether treatment with ivabradine in patients with coronary heart disease reduces the rate of cardiovascular events (such as heart attack) when compared with placebo. Patients in the study received up to 10 mg twice daily, which is higher than the currently authorized maximum daily dose (7.5 mg twice daily), and the results showed a small but significant increase in the combined risk of cardiovascular death or non-fatal heart attack with the medicine in a subgroup of patients who had symptomatic angina (Canadian Cardiovascular Society class II - IV).
The EMA will now evaluate the impact of the data from the SIGNIFY study on the balance of benefits and risks of ivabradine and issue an opinion on whether the marketing authorization should be maintained, varied, suspended or withdrawn.

Sildenafil

Clarification on warning about paediatric use for pulmonary arterial hypertension

USA. The FDA clarified its previous recommendation related to prescribing sildenafil (Revatio®) for children with pulmonary arterial hypertension (PAH). Sildenafil is FDA-approved only to treat PAH in adults, not in children; however, health-care professionals must consider whether the benefits of treatment with the drug are likely to outweigh its potential risks for each patient.

FDA revised the sildenafil drug label in August 2012, adding a warning stating that "use of sildenafil, particularly chronic use, is not recommended in children." This recommendation was based on an observation of increasing mortality with increasing sildenafil doses in a long term clinical trial in paediatric patients with PAH.

The purpose of the August 2012 recommendation was to raise awareness of clinical trial results showing a higher risk of mortality in paediatric patients taking a high dose of sildenafil when compared to paediatric patients taking a low dose. This recommendation was not intended to suggest that sildenafil should never be used in children; however, some health-care professionals have