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WHO Pharmaceuticals NEWSLETTER

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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 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®.

This issue includes recommendations from the working groups of the Thirty-eighth Annual Meeting of Representatives of National Pharmacovigilance Centres that was held in 2015, in Delhi, India.

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Safety of Medicines

Amlodipine besilate

Risk of fulminant hepatitis, agranulocytosis and rhabdomyolysis

Japan. The Ministry of Health, Labour and Welfare (MHLW) and the Pharmaceuticals and Medical Devices Agency (PMDA) have advised that the package inserts for amlodipine and amlodipine combinations containing: azilsartan; aliskiren fumarate; irbesartan; telmisartan; candesartan; valsartan; and atorvastatin calcium hydrate should list: fulminant hepatitis; agranulocytosis (except for preparations with candesartan and valsartan); and rhabdomyolysis as clinically significant adverse reactions.

Amlodipine is indicated for hypertension and angina pectoris. Amlodipine in combination with atorvastatin is used in patients with hypercholesterolemia or familial hypercholesterolemia in addition to hypertension or angina pectoris. The remaining combination products listed above are indicated for hypertension only.

Two cases of fulminant hepatitis, one case of agranulocytosis, and three cases of rhabdomyolysis have been reported in patients taking amlodipine in Japan during the last three years. A causal relationship could not be ruled out in some of these cases. In addition, there were a total of six cases of rhabdomyolysis reported in patients taking the amlodipine and atorvastatin combination. Following investigations and advice from experts, the MHLW/PMDA have decided that revision of the package insert is necessary.

Reference:
Revision of Precautions, MHLW/PMDA, 12 January 2016 (*www.pmda.go.jp/english/*)

Antiretroviral medicines

Updated advice on body-fat changes and lactic acidosis

The United Kingdom. The Medicines and Healthcare Products Regulatory Agency (MHRA) has notified health-care professionals that the product information for antiretrovirals will be updated to reflect current knowledge about lipodystrophy and lactic acidosis.

Class warnings about lipodystrophy (lipatrophy, lipoaccumulation, changes in weight and metabolism) were being routinely applied to all antiretroviral agents, and warnings of lactic acidosis were applied to nucleoside and nucleotide analogue medicines. These warnings may not accurately reflect current scientific understanding.

Following an EU-wide review, it was noted that lipoatrophy was related only to substances with a high risk of mitochondrial toxicity (zidovudine, stavudine, didanosine), and not seen in regimens with other nucleoside reverse transcriptase inhibitor products. In addition, evidence of disproportional body-fat redistribution in relation to antiretroviral treatment was not clear. Effects on blood lipids and glucose may occur with any HIV medicine and are not restricted to protease inhibitors, nucleoside and nucleotide analogues. The risk of lactic acidosis was considered to differ across nucleoside and nucleotide analogues, being most strongly associated with zidovudine, stavudine, and didanosine.

To be consistent with current HIV treatment guidelines and evidence, product information will be amended by:

- including advice that weight gain and metabolic changes (such as lipid and glucose increases) may occur during treatment with any HIV medicine. However, these changes are partly linked to underlying disease control and lifestyle in addition to antiretroviral treatment;
- retaining warnings for lipoatrophy and lipoaccumulation only for zidovudine, stavudine, and didanosine;
- removing warnings about lactic acidosis for nucleoside and nucleotide analogues, with the exception of products that contain zidovudine, stavudine, or didanosine.

Reference:
Drug Safety Update, MHRA, Volume 9, issue 5: 14 December 2015 (*www.gov.uk/mhra*)

Atovaquone

Cases of agranulocytosis and leukopenia

Japan. The MHLW and the PMDA have announced that the product labels for atovaquone (Samitrel®) and atovaquone/ proguanil combination (Malarone®) have been revised to include agranulocytosis and leukopenia as adverse reactions.

Atovaquone as a single agent is indicated for the treatment and prevention of pneumocystis pneumonia. In combination with proguanil hydrochloride, it is used in the prophylaxis and treatment of malaria.

A total of 11 cases of agranulocytosis and leukopenia have been reported in patients taking atovaquone. The causal relationship to atovaquone could not be ruled out in five of these cases. Two cases were fatal (a causal relationship could not be established). Following investigations and advice from experts, the MHLW/PMDA decided that revision of the package insert was necessary.

"Agranulocytosis and leukopenia" have been added to the "Clinically significant adverse reaction" section of the product label for atovaquone and in the "pancytopenia" subsection in the atovaquone/ proguanil preparation.

Reference:
Revision of Precautions, MHLW/PMDA, 12 January 2016 (*www.pmda.go.jp/english/*)

Azilsartan

Risk of rhabdomyolysis

Japan. The MHLW and the PMDA have announced that the product information for azilsartan (Azilva®) and azilsartan/amlodipine preparation (Zacras®) have been revised to include rhabdomyolysis as an adverse effect.

Azilsartan is an angiotensin II receptor antagonist used in the treatment of hypertension. In Japan, a total of five cases in patients taking azilsartan as a single preparation associated with rhabdomyolysis have been reported (including four cases for which a causal relationship to the product could not be ruled out). One case of rhabdomyolysis associated with use of azilsartan/amlodipine combination has also been reported.

Following investigations and advice from experts, the MHLW/PMDA decided that changes to the package insert were necessary. "Rhabdomyolysis" will be added in the "Clinically significant adverse reaction" section.

Reference:
Revision of Precautions, MHLW/PMDA, 12 January 2016 (*www.pmda.go.jp/english/*)

Benzoyl peroxide and salicylic acid topical products

Risk of serious allergic reactions

Canada. Health Canada has informed health-care professionals and consumers about the risk of serious hypersensitivity reactions, and changes to product information for over-the-counter (OTC) topical acne products containing either benzyl peroxide or salicylic acid.

Health Canada has conducted a health review and concluded that there is evidence to support a link between the use of OTC benzyl peroxide or salicylic acid topical acne products and serious hypersensitivity reactions including anaphylaxis. Health Canada received 10 and 16 cases of serious hypersensitivity reactions to OTC benzyl peroxide and salicylic acid products respectively of which five (benzyl peroxide) and four (salicylic acid) were anaphylaxis.

As a result Health Canada will update the directions of use and warning sections of the Health Canada Acne Therapy Monograph for topical OTC acne products containing these components.

An information update will be published and will provide the following consumer advice in the event of an anaphylactic reaction:

- if you develop severe itching and hives, with swelling on the face, eyes, lips, mouth or throat; difficulty breathing, throat tightness or hoarseness; and/or fainting, please see emergency medical services.

Reference:
Summary Safety Review, Health Canada, 10 December 2015 (*www.hc-sc.gc.ca*)

Bisphosphonates

Risk of osteonecrosis of the external auditory canal

The United Kingdom. The MHRA has announced that the product information for bisphosphonates will be updated to advise health-care professionals and patients of the possibility of osteonecrosis of the external auditory canal with bisphosphonate use.

Bisphosphonates (alendronic acid, ibandronic acid, pamidronate disodium, risedronate sodium, sodium clodronate, zoledronic acid) are used to treat osteoporosis and Paget's disease, and are part of some cancer regimens (particularly metastatic bone cancer and multiple myeloma). Individual bisphosphonates have different indications.

Benign idiopathic osteonecrosis of the external auditory canal is a rare condition that can occur in the absence of antiresorptive therapy (therapy to increase bone strength) and is sometimes associated with local trauma.

At the time of the announcement, there were 29 reports of osteonecrosis of the external auditory canal in association with bisphosphonates (oral and intravenous forms) for use in both cancer related and osteoporosis indications, that have been identified globally and 11 cases reported in the literature. Most cases were associated with long term bisphosphonate therapy (≥2 years) and included possible risk factors, for example steroid use. Evidence from cases reported and from the literature supports a causal association between

bisphosphonates and osteonecrosis of the external canal, however evidence is insufficient with use of higher bisphosphonate doses for cancer-related conditions.

The MHRA provides health-care professionals with the following advice:

- The possibility of osteonecrosis of the external auditory canal should be considered in patients receiving bisphosphonates who present with ear symptoms, including chronic ear infections, or in patients with suspected cholesteatoma.
- Possible risk factors include steroid use and chemotherapy, with or without local risk factors such as infection or trauma.
- Patients should be advised to report any ear pain, discharge from the ear, or an ear infection during bisphosphonate treatment.

Reference:
Drug Safety Update, MHRA Volume 9, issue 5: 14 December 2015 (*www.gov.uk/mhra*)

Deferasirox

Risk of pancreatitis in paediatric patients

Singapore. The Health Sciences Authority (HSA) has announced that the package insert for deferasirox (Exjade®) will be strengthened to include warnings on the risk of acute pancreatitis.

Deferasirox is an oral iron chelator used for treatment of chronic iron overload due to: frequent blood transfusions (patients aged ≥6 years, or 2-years if other treatments are contraindicated), beta thalassaemia (patients aged ≥10 years), and non transfusion dependant thalassaemia syndromes.

Acute pancreatitis is characterized by an increase in pancreatic enzymes in the blood and urine.

A signal of pancreatitis associated with deferasirox was published in June 2015. There have been 14 reports globally in children and adolescents aged 2-16 years (until March 2015), for this suspected adverse reaction.

Health-care professionals are advised to take into consideration the potential risk of acute pancreatitis in patients who are prescribed deferasirox, and to monitor for signs and symptoms which could be suggestive of pancreatitis, such as abdominal pain, nausea, vomiting or tenderness of the abdomen to touch, particularly in paediatric patients.

(See WHO Pharmaceuticals Newsletter No.6, 2015: Signal-Deferasirox and pancreatitis in paediatric patients)

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

Elvitegravir/ cobicistat/ emtricitabine/ tenofovir disoproxil fumarate and anti-epileptic medications

Potential reduction of blood concentration by drug-drug interaction

Japan. The MHLW and the PMDA have announced changes in the product label for the antiretroviral combination elvitegravir/cobicistat/ emtricitabine/tenofovir disoproxil fumarate (Stribild®) to include warnings of the interaction between Stribild® and carbamazepine, phenobarbital, phenytoin, fosphenytoin (phenytoin prodrug). Stribild® is indicated for the treatment of human immunodeficiency virus-1 (HIV-1) infection.

The results of a clinical trial have shown that concomitant use of carbamazepine significantly reduces blood concentrations of elvitegravir and cobicistat, which could result in loss of therapeutic effect. Phenobarbital and phenytoin are also potent inducers of CYP3A comparable to carbamazepine. Based on available evidence and advice from experts, the MHLW/PMDA have decided that it was necessary to revise the package insert for Stribild® as follows:
"Carbamazepine, phenobarbital, phenytoin, fosphenytoin" should be added to the contraindications section under "Patients being administered the following drugs". "Carbamazepine, phenobarbital, phenytoin" should be deleted from Precautions for concomitant use subsection, and added to the "Contraindications for concomitant use" subsection in the "Interactions" section.

Reference:
Revision of Precautions, MHLW/PMDA, 24 November 2015 (*www.pmda.go.jp/english/*)

Fluoroquinolones oral antibiotics

Risk of retinal detachment

Canada. Health Canada recommends that product labels for oral fluoroquinolones should be revised to highlight the urgency of seeking advice from health-care professionals if patients experience vision problems during or following use of fluoroquinolones.

Retinal detachment is a painless separation of the retina from the layer of

support tissue and blood vessels at the back of the eye that provide the retina with oxygen and nourishment. Retinal detachment is a medical emergency and symptoms include sudden appearance of debris in the field of vision, the perception of flashes of light in the affected eye, sensation of a shadow or curtain over the portion of the visual field, and sudden or complete loss of vision.

Oral fluoroquinolones (ciprofloxacin, levofloxacin, moxifloxacin, norfloxacin, and ofloxacin) are used to treat bacterial infections, in particular respiratory and urogenital system infections. The recommendations follow a follow-up review of evidence. At the time of the review 22 reports of retinal detachment linked to oral fluoroquinolones were reported internationally, and three reports were received in Canada. A causal relationship between the Canadian reports could not be established. In the literature two of four observational studies found a modest link between retinal detachments and use of fluoroquinolones. Health Canada concluded that a link cannot be ruled out at present.

Reference:
Summary Safety Review, Health Canada, 8 January 2016 (*www.hc-sc.gc.ca*)

Japan, there have been a number of reported adverse reactions including fatal cases, but no cases associated with anaphylaxis. Based on available evidence and advice of experts, the MHLW/PMDA have decided that it was necessary to revise the package insert.

"Anaphylaxis" will be added to the "Clinically significant adverse reaction" subsection in the "adverse reaction" section in the package insert.

Reference:
Revisions of Precautions, MHLW/PMDA, 24 November 2015 (*www.pmda.go.jp/english/)*

Fingolimod

Recommendations to minimise progressive multifocal leukoencephalopathy (PML) and skin cancer

EU: The European Medicines Agency (EMA) has announced that product information for fingolimod (Gilenya®) will be updated with information about risk of progressive multifocal leukoencephalopathy (PML) and basal cell carcinoma.

Fingolimod is used to treat multiple sclerosis and works by reducing activity of the immune system, in particular T-cells which are involved in fighting infection.

There have been 151 international cases of basal cell carcinoma reported with exposure to fingolimod (February 2015).

The EMA recommends that patients should be evaluated before and during treatment with fingolimod to allow early identification of signs and symptoms that could be linked to PML or basal cell carcinoma and they should be treated accordingly. Before starting treatment with fingolimod, a baseline MRI scan should be available (usually within three months) as a reference. If PML is suspected, a MRI should be performed immediately and treatment with fingolimod should be suspended until PML has been excluded. With regard to the risk of basal cell carcinoma, a medical evaluation of the skin is recommended before starting treatment, after at least one year and then at least yearly during treatment. Fingolimod must not be used in patients with basal cell carcinoma, or any other type of cancer.

(See WHO Pharmaceuticals Newsletter No.5, 2015: Risk of progressive multifocal leukoencephalopathy in USA and Japan.)

Reference:
Press release, EMA, 18 December 2015 (*http://www.ema.europa.eu/*)

Interferon beta-1a