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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 newsletter includes three feature articles describing: WHO-UMC-HSA Inter-Regional Pharmacovigilance Training in Singapore; the 2nd annual meeting for strengthening pharmacovigilance in Eastern Mediterranean region; and capacity building workshop in the Republic of Congo.

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Amantadine hydrochloride

Risk of rhabdomyolysis

Japan. The Ministry of Health, Labour and Welfare (MHLW) and the Pharmaceuticals and Medical Devices Agency (PMDA) have announced the revision of the package insert for amantadine hydrochloride (Symmetrel®) to include risk of rhabdomyolysis.

Amantadine hydrochloride (Symmetrel®) is used for Parkinson's disease, improvement of hypobulia or decreased initiative associated with sequela of cerebral infarction and Type A influenza virus infection in Japan.

The MHLW/PMDA stated that one case of rhabdomyolysis has been reported in a patient treated with amantadine hydrochloride in Japan. A causal relationship to the product could not be ruled out.

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

Rhabdomyolysis:
Rhabdomyolysis may occur. Patients should be carefully monitored. If symptoms including myalgia, feelings of weakness, increased creatine kinase (creatine phosphokinase), or increased blood and urine myoglobin are observed, administration of this drug should be discontinued and appropriate measures should be adopted. In addition, caution should be exercised for development of acute renal failure due to rhabdomyolysis.

Reference:
Revision of Precautions, MHLW/PMDA, 15 September 2015 (*www.pmda.go.jp/english/*)

Asunaprevir and daclatasvir

Risk of thrombocytopenia

Japan. The MHLW and the PMDA have announced the revision of the package insert for asunaprevir (Sunvepra®) and daclatasvir (Daklinza®) to include risk of thrombocytopenia.

Asunaprevir and daclatasvir as a combination are used for the treatment of chronic hepatitis C virus (HCV) infection, in patients with serogroup 1 (genotype 1), or compensated cirrhosis type C.

The MHLW/PMDA stated that cases of thrombocytopenia have been reported in patients treated with asunaprevir and daclatasvir hydrochloride in Japan.

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

Thrombocytopenia:
Thrombocytopenia may occur. Patients should be carefully monitored through periodic blood tests, etc. If any abnormalities are observed, appropriate measures such as discontinuation of administration should be adopted.

Reference:
Revision of Precautions, MHLW/PMDA, 15 September 2015 (*www.pmda.go.jp/english/*)

Azithromycin hydrate

Risk of drug-induced hypersensitivity syndrome

Japan. The MHLW and the PMDA have announced the revision of the package insert for azithromycin hydrate (Zithromac®) to include risk of drug-induced hypersensitivity syndrome.

Azithromycin hydrate is used for treatment of infections caused by microorganisms sensitive to azithromycin.

The MHLW/PMDA stated that cases of drug-induced hypersensitivity syndrome or drug rash with eosinophilia and systemic syndrome have been reported in patients treated with azithromycin hydrate both in Japan and in other countries. In addition, the company core datasheet (CCDS) has been updated.

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

Drug-induced hypersensitivity syndrome (DIHS):
Rash and/or pyrexia may occur as initial symptoms, followed by serious late-onset hypersensitivity symptoms with hepatic function disorder, lymphadenopathy, increased white blood cells, increased eosinophils, atypical lymphocytes, etc. Patients should be carefully monitored. If such symptoms are observed, administration of this drug should be discontinued and appropriate measures should be adopted. The reactivation of viruses including Human Herpes Virus 6 (HHV-6) has been frequently found associated with DIHS. Symptoms such as rash, pyrexia, and/or hepatic

function disorder may relapse or be prolonged even after discontinuation of administration, and therefore, caution should be exercised.

Reference:
Revision of Precautions, MHLW/PMDA, 15 September 2015 (*www.pmda.go.jp/english/*)

(See WHO Pharmaceuticals Newsletter No.6, 2014 for Drug Reaction/Rash with Eosinophilia and Systemic Symptoms (DRESS) in Canada)

Canagliflozin

Increased risk of bone fractures and new information on risk of decreased bone mineral density

USA. The US Food and Drug Administration (FDA) has strengthened the warning for the type 2 diabetes medicine canagliflozin (Invokana® and Invokamet®) related to the increased risk of bone fractures, and added new information relating to risk of decreased bone mineral density. To address these safety concerns, the FDA added a new Warning and Precaution and revised the Adverse Reactions section of the canagliflozin drug labels.

Canagliflozin is a prescription medicine used in combination with diet and exercise to lower blood sugar in adults with type 2 diabetes. It belongs to a class of drugs called sodium-glucose cotransporter-2 (SGLT2) inhibitors. Canagliflozin is available as a single-ingredient product and also in combination with the diabetes medicine metformin.

The FDA is continuing to evaluate the risk of bone fractures with other drugs in the SGLT2 inhibitor class, including dapagliflozin and empaglifozin, to determine if additional label changes or studies are needed. Health-care professionals and patients are urged to report side effects involving canagliflozin or other SGLT2 inhibitors.

The FDA has recommended that health-care professionals should consider factors that contribute to fracture risk prior to starting patients on canagliflozin and that patients should talk to their health-care professionals about factors that may increase the risk for bone fracture. Patients should not stop or change their diabetes medicines without first talking to their health-care professional.

Reference:
Drug Safety Communication, US FDA, 10 September 2015 (*www.fda.gov*)

Clozapine

Modifications for monitoring neutropenia

USA. The US FDA has changed the requirements for monitoring, prescribing, dispensing, and receiving clozapine, to address continuing safety concerns of severe neutropenia (dangerously low number of neutrophils and white blood cells).

Clozapine is an antipsychotic medicine used to treat symptoms of schizophrenia in patients who do not respond adequately to standard antipsychotic treatment. It is also effective in reducing risk of repeated suicidal behaviour in patients with schizophrenia or schizoaffective disorder.

The changes include: Modification of the prescribing information for clozapine to clarify and enhance explanations on how to monitor for neutropenia and manage clozapine treatment, and approval of a shared risk evaluation and mitigation strategy (REMS) called the Clozapine REMS Program. The shared REMS is expected to reduce the burden and possible confusion related to having separate registries for individual clozapine medicines.

The FDA has informed that patients who are currently treated with clozapine will be automatically transferred to the Clozapine REMS Program. Prescribers and pharmacies that dispense clozapine will be required to be certified in the Clozapine REMS Program according to a specific transition schedule starting 12 October 2015.

Reference:
Drug Safety Communication, US FDA, 15 September 2015 (*www.fda.gov*)

Deferasirox

Risk of gastrointestinal perforations

Japan. The MHLW and the PMDA have announced the revision of the package insert for deferasirox (Exjade®) to include risk of gastrointestinal perforations.

Deferasirox is indicated for chronic iron overload due to blood transfusions (when iron chelating agents such as desferrioxamine is contraindicated or inadequate).

The MHLW/PMDA stated that cases of gastrointestinal perforations have been reported in patients treated with deferasirox both in Japan and other countries and that the CCDS has been updated.

Based on expert advice and available evidence, the MHLW/PMDA have recommended the addition of the "gastrointestinal perforations" to the subsection of "Gastric ulcer (including multiple ulcers), duodenal ulcer, and gastrointestinal haemorrhage" in the section of

"Clinically significant adverse reaction" in the package insert.

Reference:
Revision of Precautions, MHLW/PMDA, 6 August 2015 (*www.pmda.go.jp/english/*)

Fingolimod

1. Risk of progressive multifocal leukoencephalopathy (PML)

USA and Japan. The US FDA, the MHLW and the PMDA have announced label changes for fingolimod (Gilenya® and Imusera®). The changes inform health-care professionals and the public of two cases of progressive multifocal leukoencephalopathy (PML) reported in patients with multiple sclerosis (MS) that were treated with fingolimod.

These are the first cases of PML reported in patients taking fingolimod, who had not been previously treated with an immunosuppressant drug for MS or any other medical condition.

Fingolimod is an immunomodulator shown to benefit patients with relapsing forms of MS.

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

Progressive multifocal leukoencephalopathy (PML): PML may occur. Patients should be carefully monitored during and after treatment with this drug. If symptoms such as disturbed consciousness, cognitive disorder, symptoms of paralysis (hemiplegia or quadriplegia), or speech and language disorder are observed, imaging diagnostics with MRI and cerebrospinal fluid tests should be performed. In addition, administration of this drug should be discontinued, and appropriate measures should be adopted.

The FDA has recommended that health-care professionals should stop fingolimod and perform a diagnostic evaluation if PML is suspected.

References:
Drug Safety Communication, US FDA, 4 August 2015 (*www.fda.gov*)
Revision of Precautions, MHLW/PMDA, 15 September 2015 (*www.pmda.go.jp/english/*)

2. Risk of abnormal tissue growth (neoplasms)

Canada. The Canadian product monograph for fingolimod has been updated to include information on an increased risk of lymphomas and other malignant cancers (particularly the skin) following results of a safety review. Health Canada has requested additional safety information from the manufacturer and will continue to monitor this issue.

At the time of the review, there were 16 reports of neoplasms linked to fingolimod in Canada. The World Health Organization (WHO) global database of individual case safety reports (ICSRs), VigiBase® presented 62 cases of skin cancer at the time of the review.

A review of the scientific and medical literature identified two published case reports, three clinical trials, and four safety reviews that describe cases of neoplasms in patients treated with fingolimod. In two of the clinical trials, participants receiving fingolimod had a higher occurrence of skin cancers than those who did not.

Numerous patient medical reports received from the manufacturer link skin cancer to fingolimod since it was first approved for sale. In addition, reports of skin cancer have increased recently in patients treated with fingolimod.

Adverse effects such as neoplasms are rare and could take a long time to develop or be detected. Therefore, additional safety information from the manufacturer of fingolimod about the risk of neoplasms has been requested by Health Canada. Furthermore, Health Canada will continue to monitor adverse event information involving fingolimod.

Reference:
Summary Safety Review, Health Canada, 14 September 2015 (*www.hc-sc.gc.ca*)

Hydroxyzine-containing medicines

Risk of prolonged QT interval and ventricular tachycardia

Japan. The MHLW and the PMDA have announced the revision of the package insert for hydroxyzine-containing medicines (Atarax®) to include risk of prolonged QT interval and ventricular tachycardia.

Hydroxyzine-containing medicines are used for urticaria, pruritus associated with skin disease, anxiety, tension, depressed mood in neurosis.

The MHLW/PMDA stated that cases of prolonged QT interval and ventricular tachycardia have been reported in patients treated with hydroxyzine-containing medicines in Japan and in other countries. In addition, European Medicines Agency (EMA) have taken

action to minimize the risks of effects on heart rhythm with hydroxyzine-containing medicines.

Based on expert advice and available evidence, the MHLW/PMDA have recommended the addition of "Patients with prolonged QT interval (including those with long QT interval syndrome congenital), patients being administered drugs known to prolong QT interval, and patients with significant bradycardia or hypokalaemia" to the section of the "Careful administration" in the package insert.

The MHLW/PMDA also recommended the addition of the following text to the subsection of the "Clinically significant adverse reaction" in the section of "Adverse reaction" in the package insert.

QT interval prolongation and ventricular tachycardia (including torsades de pointes):
QT interval prolongation or ventricular tachycardia (including torsades de pointes) may occur. Patients should be carefully monitored. If any abnormalities are observed, administration of this drug should be discontinued and appropriate measures should be adopted.

Reference:
Revision of Precautions, MHLW/PMDA, 6 August 2015 (*www.pmda.go.jp/english/*)

(See WHO Pharmaceuticals

Infliximab

Risk of non-melanoma skin cancers, particularly in psoriasis patients

Australia. The Therapeutic Goods Administration (TGA) has announced that the Product Information for infliximab has been updated to provide further information about the risk of skin cancers, particularly in psoriasis patients who have undergone phototherapy.

Infliximab (Remicade®) is a chimeric human-murine monoclonal antibody that binds to human tumour necrosis factor alpha (TNFα) and is indicated for treatment of rheumatoid arthritis in adults, ankylosing spondylitis, psoriatic arthritis, psoriasis, Crohn's disease, refractory fistulising Crohn's disease and ulcerative colitis.

The changes included updating the 'Precautions' section to include the statement 'Psoriasis patients should be monitored for non-melanoma skin cancers (NMSCs), particularly those patients who have had prior prolonged phototherapy treatment.

In addition, basal cell carcinoma and squamous cell carcinoma were added to the 'Adverse events' section with the frequency listed as unknown.

The TGA has reminded prescribers to monitor patients

Ingenol mebutate gel

Risk of severe allergic reactions and herpes zoster (shingles)

USA. The US FDA has requested that the product label for Ingenol mebutate gel (Picato®) is updated to include a warning of an increased risks of severe allergic reactions and herpes zoster (shingles). In addition, instructions on the safe an appropriate application of the gel should also be provided.

Ingenol mebutate is used to treat actinic keratosis, a scaly, crusty lesion on the skin that may be red or yellow in colour.

The FDA has received reports of cases of severe eye injuries and skin reactions associated with the application of ingenol mebutate gel. Some cases were associated with ingenol mebutate gel not being used according to the instructions for use on the label.

The FDA has recommended that patients who experience a severe allergic reaction should stop using ingenol mebutate gel and seek immediate medical attention. The allergic reaction may include throat tightness, difficulty breathing, feeling faint, or swelling of the lips or tongue. The FDA also recommended that patients should stop using the product and contact a health-care professional if they develop hives, itching, or severe skin