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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®.

The Summary of Recommendations from the Twelfth Meeting of the WHO Advisory Committee on Safety of Medicinal Products (ACSoMP) is included as a feature item together with a small article from the Food and Drugs Authority in Ghana on patient reporting of adverse reactions.

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Regulatory Matters

Safety of medicines

Abiraterone acetate

Risk of fulminant hepatitis and hepatic failure

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 abiraterone acetate (Zytiga®) to include risk of fulminant hepatitis and hepatic failure.

Abiraterone acetate is indicated for castration-resistant prostate cancer.

The MHLW/PMDA stated that cases of fulminant hepatitis or hepatic failure have been reported in patients treated with abiraterone acetate in Japan.

Based on expert advice and available evidence, the MHLW/PMDA have recommended the addition of the description on the risk of fulminant hepatitis and hepatic failure to the information on hepatic function disorder in the section of "Important precaution" and to the subsection of the "Clinically significant adverse reactions" in the section of "Adverse reactions" in the package insert.

Reference:
Revision of Precautions, MHLW/PMDA, 7 July 2015 (*www.pmda.go.jp/english/*)

Adefovir pivoxil

Risk of fracture

Japan. The MHLW and the PMDA have announced the revision of the package insert for adefovir pivoxil (Hepsera®) to include risk of fracture.

Adefovir pivoxil is indicated for the inhibition of hepatitis B virus replication in type B chronic liver disease in which abnormality of liver function with replication of hepatitis B virus is confirmed.

The MHLW/PMDA stated that cases of fractures have been reported in patients treated with adefovir pivoxil in Japan.

Based on expert advice and available evidence, the MHLW/PMDA have recommended adding risk of fracture to the section of "Important precautions" and to the subsection of the "Clinically significant adverse reactions" in the section of "Adverse reactions" in the package insert.

Reference:
Revision of Precautions, MHLW/PMDA, 7 July 2015 (*www.pmda.go.jp/english/*)

Anagliptin

Risk of intestinal obstruction

Japan. The MHLW and the PMDA have announced the revision of the package insert for anagliptin (Suiny®) to include risk of intestinal obstruction.

Anagliptin is indicated for type 2 diabetes mellitus.

The MHLW/PMDA stated that cases associated with intestinal obstruction have been reported in patients treated with anagliptin in Japan.

Based on expert advice and available evidence, the MHLW/PMDA have recommended the addition of "Patients who have a history of abdominal surgery or intestinal obstruction" to the section of "Careful administration" in the package insert and the addition of the following texts to the subsection of the "Clinically significant adverse reactions" under "Adverse reactions" in the package insert.

Intestinal obstruction: Intestinal obstruction may occur. Patients should be carefully monitored. If any abnormalities such as severe constipation, abdominal distension, sustained abdominal pain, or vomiting are observed, administration of this drug should be discontinued, and appropriate measures should be adopted.

Reference:
Revision of Precautions, MHLW/PMDA, 7 July 2015 (*www.pmda.go.jp/english/*)

Asunaprevir and daclatasvir hydrochloride

Risk of hepatic failure

Japan. The MHLW and the PMDA have announced the revision of the package inserts for asunaprevir (Sunvepra®) and daclatasvir hydrochloride (Daklinza®) to include risk of hepatic failure.

Asunaprevir and daclatasvir hydrochloride are used for improvement of viraemia in patients with serogroup 1 (genotype I) chronic hepatitis C or compensated cirrhosis type C.

The MHLW/PMDA stated that cases of decreased hepatic residual function such as decreased albumin level, prolonged prothrombin time, ascites, hepatic encephalopathy, and those resulting in hepatic failure 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 an alert on decreased hepatic residual function to the

subsection relevant to "the assessment of hepatic function" in the section of "Important precautions" and the addition of hepatic failure to the subsection of the "hepatic function disorder" in the section of "Clinically significant adverse reactions section" in the package insert.

Reference:
Revision of Precautions, MHLW/PMDA, 7 July 2015 (*www.pmda.go.jp/english/*)

Crizotinib

Risk of cardiac failure

Japan. The MHLW and the PMDA have announced the revision of the package insert for crizotinib (Xalkori®) to include risk of cardiac failure.

Crizotinib is indicated for *Anaplastic lymphoma kinase (ALK)*-positive, unresectable, advanced or relapsed non-small-cell lung cancer.

The MHLW/PMDA stated that cases of cardiac failure have been reported in patients treated with crizotinib in Japan.

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

Cardiac failure:
Cardiac failure may occur. Patients should be carefully monitored. If the fluid retention (pulmonary oedema, pleural effusion, pericardial effusion, etc.), rapid increased weight, cardiac failure symptoms (shortness of breath, dyspnoea, oedema, etc.) are observed, appropriate measures such as drug suspension, dose reduction, or discontinuation of administration, should be adopted.

Reference:
Revision of Precautions, MHLW/PMDA, 2 June 2015 (*www.pmda.go.jp/english/*)

Denosumab

Further measures to minimise risk of osteonecrosis of the jaw

UK. The Medicines and Healthcare Products Regulatory Agency (MHRA) has reminded health-care professionals to advise patients to take precautionary measures to minimise the risk of osteonecrosis of the jaw (ONJ) in patients taking denosumab and intravenous bisphosphonates.

Denosumab and bisphosphonates are used to treat osteoporosis, Paget's disease, and as part of some cancer regimens, particularly for metastatic bone cancer and multiple myeloma. Individual bisphosphonates and denosumab-containing medicines have different indications (information available in the summary of product characteristics (SmPC) of the medicine in question).

The advice follows a review conducted by MHRA and other EU medicines regulators. Patients should be advised to: maintain good oral hygiene, attend routine dental check-ups and immediately report any oral symptoms such as dental mobility, pain, or swelling to a doctor and dentist before being prescribed oral bisphosphonates. Further recommendations include: introducing patient reminder cards for denosumab and intravenous bisphosphonates, to inform patients of the risk of ONJ and precautions to take before and during treatment; denosumab 120 mg should be contraindicated in patients with unhealed lesions from dental or oral surgery. Patient reminder cards about the risk of are being introduced.

Reference:
Drug Safety Update, MHRA, Volume 8, issue 12: 1, July 2015 (*www.gov.uk/mhra*)

(See WHO Pharmaceuticals Newsletter No.6, 2014 for Risk of osteonecrosis of the jaw and hypocalcaemia in Egypt)

Dimethyl fumarate

Risk of serious allergic reactions including skin reactions and anaphylaxis

Canada. Canadian prescribing information for dimethyl fumarate has been updated to inform prescribers and patients of hypersensitivity reactions, including angioedema and anaphylaxis. However, following a safety review, Health Canada has concluded that the overall benefits of dimethyl fumarate (Tecfidera®) continue to outweigh the risks if used as recommended.

The Canadian prescribing information was also updated to mention that the possibility of hypersensitivity or anaphylactic reactions should be considered in patients experiencing severe flushing reactions (e.g. flushing, hot flushes, warmth, redness, itching, and/or burning sensations). These symptoms may present similarities with hypersensitivity reactions.

Dimethyl fumarate is used to reduce the number of flare-ups (relapses) and slow the progression of physical disability in multiple sclerosis.

At the time of this review, Health Canada considered the evidence provided in both domestic (nine reports) and international reports (five reports), including those

provided by the product manufacturer, of hypersensitivity associated with dimethyl fumarate.

Overall, the number of hypersensitivity reactions reported has increased for dimethyl fumarate, with some reports being life-threatening. This increase may be due to a greater use of dimethyl fumarate.

Reference:
Summary Safety Review, Health Canada, 26 June 2015 (*www.hc-sc.gc.ca*)

Ethinylestradiol /etonogestrel vaginal ring

Thromboembolic risk

Australia. The Therapeutic Goods Administration (TGA) has advised health-care professionals that the Product Information for ethinylestradiol/etonogestrel vaginal ring (NuvaRing®) has been updated to provide further information about thromboembolic risks.

Ethinylestradiol/etonogestrel vaginal ring is a contraceptive ring for vaginal use, which releases ethinylestradiol and etonogestrel over a period of three weeks.

While ethinylestradiol/ etonogestrel vaginal ring is delivered vaginally, the active ingredients are the same as combined hormonal oral contraceptives, and the risks of arterial and venous thromboembolism (ATE and VTE) are similar for all of these products. It is possible that the risk of VTE may also increase with the presence of superficial thrombophlebitis and varicose veins.

Ethinylestradiol/etonogestrel vaginal ring should not be used in the presence of any of the following conditions:

- Presence or history of ATEs or VTEs, such as deep venous thrombosis, pulmonary embolism or myocardial infarction, or of a cerebrovascular accident.
- Known predisposition for ATE or VTE.
- Presence or history of prodromi of a thrombosis, for example transient ischaemic attack or angina pectoris.
- History of migraine with focal neurological symptoms.
- Diabetes mellitus with vascular involvement.

Presence of severe or multiple risk factor(s) for ATE or VTE may also constitute a contraindication.

If any of the above conditions appear for the first time during the use of ethinylestradiol/ etonogestrel vaginal ring, it should be removed immediately.

Reference:
Medicines Safety Update, TGA, Vol. 6, No. 3, June 2015 (*www.tga.gov.au*)

(See WHO Pharmaceuticals Newsletters No.6, 2013, No.4, 2013 and No.6, 2004 for related information)

Ferumoxytol

Risk of serious allergic reactions

Canada. Health Canada has announced that the Canadian prescribing information for ferumoxytol (Feraheme®) has been updated with advice to avoid giving ferumoxytol in patients with a history of drug allergies, and on how it should be given to reduce the risk of serious hypersensitivity reactions.

Health Canada issued both a health-care professional and a public communication stating limitations for ferumoxytol use. Ferumoxytol should not be used in patients with allergies to injectable iron products or with multiple drug allergies. Another communication for health-care professionals was issued with advice on how to minimise the risk of serious hypersensitivity reactions during ferumoxytol administration.

Ferumoxytol is an injectable iron product used to treat low levels of iron in the blood (iron deficiency anaemia) in adults with chronic kidney disease.

This advice follows a safety review conducted to determine if current strategies to minimize the risk were sufficient.

As of February 28, 2014, there were more than 20 Canadian reports of serious hypersensitivity reactions, including 2 deaths, received through the Canada Vigilance Program. Over half were reported in a 6 month period.

Many of the international cases of serious or fatal hypersensitivity reactions reported with ferumoxytol, also documented patients as having allergies to other medicines.

Reference:
Summary Safety Review, Health Canada, 3 July 2015 (*www.hc-sc.gc.ca*)

(See WHO Pharmaceuticals Newsletters No.3, 2015 for Risk of fatal allergic reactions in the US, No.5, 2014 for Risk of serious hypersensitivity reactions in the UK and No.4, 2014 for New restrictions in Canada)

Fusidic acid and HMG-CoA reductase inhibitors

Risk of rhabdomyolysis by drug-drug interaction

Ireland. The Health Products Regulatory Authority (HPRA) has stated that cases of

rhabdomyolysis (including some with a fatal outcome) suspected to be due to an interaction between fusidic acid and a HMG-CoA reductase inhibitor (collectively known as "statins") have been reported to the HPRA and other European medicines agencies. The exact mechanism for this interaction is unknown and therefore may occur with some, or all, statins. The product information for systemic fusidic acid indicates that concomitant treatment with statins is contraindicated, while the product information for the individual statins highlights the need to temporarily discontinue statin therapy when treatment with fusidic acid is considered essential.

Statins are a class of medicines used as an adjunct to diet for the treatment of hypercholesterolaemia, when the response to diet and other non-pharmacological treatments (e.g. exercise, weight reduction) is inadequate. They are also authorised as an adjunct to treatment in the secondary prevention of major cardiac events in patients with cardiovascular disease.

Fusidic acid and its salts (including sodium fusidate) are antistaphylococcal agents used for the treatment of serious or deep-seated infections requiring good tissue or bone penetration, such as osteomyelitis. Systemic

Ibuprofen

Small increased cardiovascular risk with daily doses at or above 2,400mg

Ireland. The HPRA has announced that the product information for all systemic ibuprofen containing products will be updated as soon as possible to reflect small increased cardiovascular risk with daily doses at or above 2,400mg.

Ibuprofen is a non-steroidal anti-inflammatory drug (NSAID) commonly used for the reduction of pain, inflammation and fever.

The most recent EU review completed by the Pharmacovigilance Risk Assessment Committee (PRAC) has confirmed a small increase in the risk of arterial thrombotic events (e.g. myocardial infarction or stroke) in patients taking high doses of ibuprofen (at or above 2,400mg/day).

The HPRA has advised health-care professionals that:

- Ibuprofen should be prescribed at the lowest dose for the shortest duration possible.
- Patients with uncontrolled hypertension, congestive heart failure (NYHA II-III), established ischaemic heart disease, peripheral arterial disease, and/or cerebrovascular disease

ibuprofen (2400 mg/day) are required.

Reference:
Drug Safety Newsletter, HPRA, June 2015

(See WHO Pharmaceuticals Newsletter No.3, 2015 for Risk of serious heart and stroke adverse events at high doses in Canada)

Indapamide

Risk of Toxic epidermal necrolysis (TEN)

Japan. The MHLW and the PMDA have announced the revision of the package insert for indapamide (Natrix® and Tenaxil®) to include risk of toxic epidermal necrolysis (TEN).

Indapamide is indicated for Essential hypertension.

The MHLW/PMDA stated that cases of TEN have been reported in patients treated with indapamide in Japan.

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

Reference:
Revision of Precautions, MHLW/PMDA, 7 July 2015 (*www.pmda.go.jp/english/*)