World Health Organization

WHO Pharmaceuticals NEWSLETTER

2015 No. 1

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:

Safety and Vigilance,

EMP-HIS,
World Health Organization,
1211 Geneva 27, Switzerland,
E-mail address: pals@who.int

This Newsletter is also available on our Internet website:
http://www.who.int/medicines

Further information on adverse reactions may be obtained from the WHO Collaborating Centre for International Drug Monitoring
Box 1051
751 40 Uppsala
Tel: +46-18-65.60.60
Fax: +46-18-65.60.80
E-mail: info@who-umc.org
Internet: http://www.who-umc.org

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®.

Contents

Printed by the WHO Document Production Services, Geneva, Switzerland

Table of Contents

Regulatory Matters

Safety of medicines

Signal

Amoxicillin containing products

Risk of erythroderma (dermatitis exfoliative) and meningitis aseptic

Japan. The Ministry of Health Labour and Welfare (MHLW) and the Pharmaceutical and Medical Devices Agency (PMDA) announced that revision of the package insert for amoxicillin containing products was necessary.

Amoxicillin is an antibiotic and used for the treatment of a number of bacterial infections.

The MHLW/PMDA informed that cases of erythroderma (dermatitis exfoliative) have been reported in patients treated with amoxicillin hydrate in Japan and in other countries, and the company core datasheet (CCDS) has been revised to include information on erythroderma (dermatitis exfoliative). The MHLW/PMDA also informed that cases of aseptic meningitis have been reported in patients treated with amoxicillin hydrate in some countries, and the CCDS has been revised to include information on this event.

Based on expert advice and available evidence, the MHLW/PMDA have recommended the following changes to the package insert.

- Erythroderma (dermatitis exfoliative) should be added in the toxic epidermal necrolysis, oculomucocutaneous syndrome, erythema multiforme, and acute generalised exanthematous pustulosis subsection in the "Clinically significant adverse reactions" section.
- Aseptic meningitis should be added in the "Clinically significant adverse reactions" section.

Reference:
Revisions of precaution, MHLW/PMDA, 9 January 2015 (*http://www.pmda.go.jp/english/*)

Cabazitaxel acetonate

Serious bone marrow depression

Japan. The MHLW and the PMDA have recommended revision of the package insert for cabazitaxel acetonate (Jevtana®).

Cabazitaxel acetonate is indicated for prostate cancer.

Based on expert opinion and available evidence, the MHLW/PMDA concluded that information on bone marrow depression in the "Important precautions" section should be revised as follows:
Serious bone marrow depression may frequently occur. Caution should be exercised for the following points (a higher incidence of bone marrow depression such as neutropenia and febrile neutropenia has been reported especially in patients whose body surface area is small or in elderly patients):

- When cabazitaxel acetonate is administered, proper use of granulocyte-colony stimulating factor (G-CSF) should be considered by referring to the current guidelines or recommendations. Primary prophylaxis with G-CSF product should be considered especially in patients with risk factors for febrile neutropenia. (ex. ≥65 years, poor performance status, medical history of febrile neutropenia, potent pretreatment history such as extended radiation exposure, and bone marrow tumour cell infiltration)
- Patients should be carefully monitored by frequent laboratory tests (ex. blood tests) after administration of cabazitaxel acetonate. If any abnormalities are observed, appropriate measures such as drug suspension, dose reduction, and/or discontinuation of administration should be taken. (See Precautions of dosage and administration section)
- Careful attention should be paid especially to infection. Signs and symptoms such as decreased neutrophil counts, increased levels of C-reactive protein, and pyrexia should be monitored. If infection occurred or was aggravated, appropriate measures such as administration of antibiotics should be taken immediately. If neutropenia occurred, the current guidelines or recommendations should be referred for proper use of antibiotics.

Reference:
Revisions of precaution, MHLW/PMDA, 22 December 2014 (*http://www.pmda.go.jp/english/*)

Combined hormonal contraceptives

Difference in risk of thromboembolism between products and the importance of individual risk factors

Egypt. Egyptian Pharmaceutical Vigilance Center (EPVC) has informed about the differences in risk of thromboembolism between products and the importance of individual risk factors with combined hormonal contraceptives (CHCs).

EPVC has recommended:

- When prescribing CHCs, careful consideration should be given to the individual

woman's current risk factors, particularly those for venous thromboembolism (VTE), and the difference in risk of VTE between products.
- A woman who has been using her combined contraceptive without any problems does not need to stop using it.
- The importance of an individual woman's risk factors should be emphasised and the risk factors need to be regularly reassessed.
- Signs and symptoms of VTE and arterial thromboembolism (ATE) should be described to women when a CHC is prescribed.
- The possibility of a CHC associated thromboembolism should be considered when a woman presents with the symptoms.

Reference:
Newsletter, Egyptian Pharmaceutical Vigilance Center (EPVC), Volume 5, Issue 12, December 2014

(See WHO Pharmaceuticals Newsletters No.2, 2014 and No.6, 2013 for related information on combined hormonal contraceptives)

Dimethyl fumarate

Case of progressive multifocal leukoencephalopathy reported

USA. The US Food and Drug Administration (FDA) warns that a patient with multiple sclerosis (MS) who was being treated with dimethyl fumarate (Tecfidera®) developed a rare and serious brain infection called progressive multifocal leukoencephalopathy (PML), and later died. The patient was not taking any other drugs that affect the immune system or drugs that are thought to be associated with PML. As a result, information describing this case of PML is being added to the drug label for dimethyl fumarate.

Dimethyl fumarate is a drug used to treat relapsing forms of MS, a brain and spinal cord disease in which patients experience multiple episodes of weakness, numbness, and other nervous system signs and symptoms that partially or completely resolve over weeks or months. Patients may develop persistent symptoms and disability over time.

PML is a rare and serious brain infection caused by the John Cunningham (JC) virus. The JC virus is a common virus that is harmless in most people but can cause PML in some patients who have weakened immune systems.

The US FDA has recommended that health-care professionals should:
- Tell patients taking dimethyl fumarate to contact health-care professionals if they develop any symptoms that may be suggestive of PML. Symptoms of PML are diverse, progress over days to weeks, and include the following: progressive weakness on one side of the body or clumsiness of limbs; disturbance of vision; and changes in thinking, memory and orientation, leading to confusion and personality changes. The progression of deficits can lead to severe disability or death.
- Stop dimethyl fumarate immediately at the first sign or symptom suggestive of PML and perform an appropriate diagnostic evaluation.
- Monitor lymphocyte counts in dimethyl fumarate-treated patients according to approved labelling.

Reference:
Drug Safety Communication, US FDA, 25 November 2014 (*www.fda.gov*)

Epoetin alfa

Increased risk of pure red cell aplasia with subcutaneous administration

Australia. The Therapeutic Goods Administration (TGA) announced that product information for epoetin alfa has been updated to provide further information regarding an increased risk of pure red cell aplasia with subcutaneous administration, particularly in patients who have chronic renal disease.

Epoetin alfa (Eprex®) is a recombinant product that stimulates erythropoiesis and reduces the need for blood transfusions.

It has been identified that there is an increased risk of pure red cell aplasia with subcutaneous use of epoetin alfa, particularly in patients with chronic renal disease.

The Product Information (PI) had previously stated that pure red cell aplasia was identified post-market as a potential rare adverse event, which could occur after months to years of treatment. However, there was no mention of an association between the development of pure red cell aplasia and either chronic renal disease or the route of administration.

The PI has been updated to advise health professionals that most cases of pure red cell aplasia associated with epoetin alfa occurred in patients with chronic renal failure receiving subcutaneous administration. The subcutaneous route should only be used when intravenous access is not readily available.

Information for health professionals:

- When administering epoetin alfa to patients with chronic renal disease, the intravenous route is preferable.
- Where intravenous access is not readily available, epoetin alfa can still be administered subcutaneously, but you should be mindful of the increased risk of pure red cell aplasia in these situations.
- If pure red cell aplasia is diagnosed, epoetin alfa must be immediately discontinued and testing for erythropoietin antibodies should be considered. If erythropoietin antibodies are detected, patients should not be switched to another erythropoiesis-stimulating agent.

Reference:
Medicines Safety Update Vol 5, No. 6, December 2014, TGA (*www.tga.gov.au*)

Freeze-dried live attenuated mumps virus vaccine

Risk of Acute pancreatitis

Japan. The MHLW and the PMDA announced revisions to the package insert for freeze-dried live attenuated mumps virus vaccine.

Freeze-dried live attenuated mumps virus is used for prevention of mumps.

The MHLW/PMDA informed that cases of acute pancreatitis have been reported in persons injected with freeze-dried live attenuated mumps virus vaccine in Japan.

Based on investigation results and other available evidence, the MHLW/PMDA concluded that Precautions should be revised in the package insert and that the following texts should be added in the "Clinically significant adverse reactions" subsection of the Adverse reactions section.

Acute pancreatitis:
Acute pancreatitis may occur. Patients should be carefully monitored. If any abnormalities such as abdominal pain, pyrexia, nausea, vomiting, and increased serum amylase are observed, appropriate measures should be taken.

Reference:
Revisions of precaution, MHLW/PMDA, 9 January 2015 (*http://www.pmda.go.jp/english/*)

Galantamine hydrobromide

Acute generalised exanthematous pustulosis

Japan. The MHLW and the PMDA announced revisions to the package insert for galantamine hydrobromide (Reminyl®).

Galantamine hydrobromide is indicated for suppression for progress of dementia symptoms in mild to moderate dementia in Alzheimer's type.

The MHLW/PMDA informed that cases of acute generalised exanthematous pustulosis have been reported in patients treated with galantamine hydrobromide in some countries, and the company core data sheet has been updated. Based on investigation results and other available evidence, the MHLW/PMDA recommended adding Acute generalised exanthematous pustulosis in the "Clinically significant adverse reactions" section of the package insert.

The MHLW/PMDA concluded that the following text should be added:

Acute generalised exanthematous pustulosis:
Acute generalised exanthematous pustulosis may occur. Patients should be carefully monitored. If any abnormalities such as pyrexia, erythema, and many small pustules are observed, administration of this drug should be discontinued and appropriate measures should be taken.

Reference:
Revisions of precaution, MHLW/PMDA, 20 November 2014 (*http://www.pmda.go.jp/english/*)

Hydroxychloroquine or chloroquine

Risk of hypoglycaemia

Singapore. The Health Sciences Authority (HSA) has informed health-care professionals about the risk of hypoglycaemia associated with the use of hydroxychloroquine or chloroquine.

Hydroxychloroquine and chloroquine are anti-malarial drugs used for the suppression and treatment of malaria. Hydroxychloroquine is also indicated for the treatment of rheumatoid arthritis, juvenile chronic arthritis, discoid and systemic lupus erythematosus and dermatological conditions caused or aggravated by sunlight.

Hydroxychloroquine is known to potentiate the hypoglycaemic effects of anti-diabetic agents. However, it has been reported in the literature that the risk of hypoglycaemia with hydroxychloroquine was also observed in patients who were not on concomitant hypoglycaemic agents. Two such case reports are highlighted below in patients who were prescribed hydroxychloroquine for the treatment of rheumatic diseases.

One overseas case report described a 62-year-old male patient with rheumatoid arthritis who was on sulphasalazine, methotrexate, prednisolone and leflunomide. Two months after hydroxychloroquine 200mg daily was added to his therapy, he developed hypoglycaemia (blood glucose level 10mg/dL or 0.56mmol/L) leading to unconsciousness. This patient was assessed to have developed hypoglycaemia secondary to hydroxychloroquine therapy after all predisposing conditions (e.g., insulinoma, ethanol intake, oral anti-diabetics, exogenous insulin usage) were ruled out. A second case report involved an 80-year-old female who reportedly had four events of hypoglycaemia leading to abrupt syncope and loss of consciousness. These events had all occurred within the four-month window period during which she was taking hydroxychloroquine 400mg daily. Her concomitant medications did not include any oral anti-diabetics or insulin. Upon discontinuation of hydroxychloroquine, no recurrence of the hypoglycaemia was reported in the 24-month follow-up period.

There was also a published overseas case report of hypoglycaemia associated with the use of chloroquine. In the report, the patient's blood glucose level repeatedly fell below 36mg/dL (or 2mmol/L) despite repeated infusions with dextrose. While the dose and indication for chloroquine use was unknown, a post-mortem toxicological examination found levels of chloroquine to be within the range associated with death from chloroquine poisoning (57.2mg of chloroquine per 100g liver tissue). The authors postulated that the hypoglycaemia was associated with chloroquine poisoning.

In October 2013, following the European Medicines Agency's (EMA's) review of information available in EudraVigilance and the literature, it was recommended that the product labelling for hydroxychloroquine and chloroquine should be strengthened on the risk of hypoglycaemia associated with their use. More recently, in July 2014, Health Canada has also concluded from its assessment that there is sufficient evidence to support a causal association between hydroxychloroquine use and the onset of hypoglycaemia, including serious cases involving a loss of consciousness and hospitalisation.

HSA is working with the companies to strengthen existing warnings in the local package inserts for hydroxychloroquine- or chloroquine-containing products regarding the additional information on the risk of hypoglycaemia.

Reference:
Product Safety Alerts, HSA, 26 December 2014 (*http://www.hsa.gov.sg/*)

Hydroxyethyl starch intravenous infusions

Contraindications and warnings

UK. The Medicines and Healthcare products Regulatory Agency (MHRA) has informed that hydroxyethyl starch (HES) use is subject to new contraindications, warnings, and monitoring.

HES products are synthetic colloid solutions used for plasma volume expansion. Large randomised clinical trials have reported an increased risk of kidney dysfunction and mortality over 90 days of follow-up in patients who received HES compared with crystalloids. Because of the risks highlighted by these trials, a review of the benefits and risks of HES was started by European regulators in November 2012.

After considering all the available evidence, the EMA concluded that HES should be contraindicated in critically ill patients or patients with sepsis or burns. However, HES can be used in patients with acute blood loss, where treatment with crystalloids alone is not sufficient. As well as new contraindications, HES use will be subject to updated warnings in the information leaflets supplied with HES products.

There is a lack of robust long term safety data in patients undergoing surgical procedures and in patients with trauma. The European Union (EU) decision requires licence holders to conduct further studies.

Reference:
Drug Safety Update, MHRA, Volume 8, issue 5, A3, December 2014 (*www.mhra.gov.uk*)

Canada. Health Canada published that a safety review was initiated to evaluate the currently available information regarding the possible increased risk of kidney injury and death associated with HES solutions when compared to alternative treatments. This review was prompted by the publication of three study results with HES solutions.

The data from the 3 published studies showed an increased risk of kidney injury or death requiring kidney replacement therapy in patients receiving HES solutions in comparison to alternative treatments. These studies involved critically ill patients, including patients with a severe blood infection called sepsis. These findings

were supported by 3 additional published analyses that took into consideration a large volume of related literature on this subject (meta-analyses).

Health Canada has received 28 reports of adverse reactions suspected of being associated with HES solutions. In general, the reports lacked important details regarding the health of the patient at the time the HES solution was given, as well as the amount of HES that was administered. Among the 28 reports, there was one case of kidney failure and one case of death involving a blood clotting disorder.

Health Canada has completed its review of the available safety information and has found that there is an increased risk of kidney injury and death in critically ill patients, including patients with a severe blood infection (sepsis), who are treated with HES solutions.

Health Canada has:

- communicated on the increased risk of kidney injury and death associated with currently marketed HES solutions to both patients and health-care professionals on June 24, 2013 and July 18, 2013, respectively.
- worked with the manufacturer of HES solutions to update the prescribing information of these products to indicate that they should no longer be used in patients with
  - monitor kidney function.

Reference:
Advisories, Warnings and Recalls, Health Canada, 3 December 2014 (*www.hc-sc.gc.ca*)

(See WHO Pharmaceuticals Newsletter No.4, 2013 for Suspension of licences in UK and new boxed warning in the US)

Interferon beta products

Risk of thrombotic microangiopathy and nephrotic syndrome

Singapore. The HSA has updated health-care professionals on overseas cases of thrombotic microangiopathy (TMA) and nephrotic syndrome that have been reported with the use of interferon beta products.

Interferon beta products are approved for the treatment of relapsing multiple sclerosis (for both 22mcg/0.5mL and 44mcg/0.5mL strengths) and treatment of patients with a single demyelinating event with an active inflammatory process, who are determined to be at high risk of developing relapsing multiple sclerosis (for 44mcg/0.5mL strength only). Interferon beta (Betaferon®) is also approved for the above two indications, as well as for the treatment of secondary

February 2014, PRAC concluded that a causal association between interferon beta products and TMA and nephrotic syndrome could not be ruled out. Consequently, their product labels were updated and a Dear Health-care Professional Letter was issued to communicate these safety issues to health-care professionals in the EU.

HSA has not received any local adverse reaction reports of TMA and nephrotic syndrome associated with the use of interferon beta products. However, the local package inserts of Rebif® and Betaferon® have been strengthened to include warnings on the risk of these safety concerns.

Health-care professionals are advised to monitor and consider the possibility of TMA and nephrotic syndrome in patients treated with interferon beta products, if signs and symptoms consistent with these diagnoses are identified.

Reference:
Product Safety Alerts, HSA, 26 December 2014. (*http://www.hsa.gov.sg/*)

Egypt. EPVC has warned about the risk of TMA and nephrotic syndrome with beta interferons.

EPVC has recommended the following:

- To remain vigilant for the development of these