WHO PHARMACEUTICALS NEWSLETTER

World Health Organization

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 from the Uppsala Monitoring Centre's SIGNAL document.

This issue includes recommendations from the working groups of the thirty-sixth annual meeting of national pharmacovigilance centres that was held in Rome last year.

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Acetaminophen (Paracetamol INN)

Recommendation to discontinue prescribing and dispensing acetaminophen prescription combination drug products with more than 325 mg

USA. The U.S. Food and Drug Administration (FDA) recommended that health-care professionals discontinue prescribing and dispensing prescription combination drug products that contain more than 325 milligrams (mg) of acetaminophen per tablet, capsule or other dosage unit. There are no available data to show that taking more than 325 mg of acetaminophen per dosage unit provides additional benefit that outweighs the added risks for liver injury. Further, limiting the amount of acetaminophen per dosage unit will reduce the risk of severe liver injury from inadvertent acetaminophen overdose, which can lead to liver failure, liver transplant, and death.

Cases of severe liver injury with acetaminophen have occurred in patients who:

- took more than the prescribed dose of an acetaminophen-containing product in a 24-hour period;
- took more than one acetaminophen-containing product at the same time; or
- drank alcohol while taking acetaminophen products.

The US FDA also recommended that when a pharmacist receives a prescription for a combination product with more than 325 mg of acetaminophen per dosage unit that they contact the prescriber to discuss a product with a lower dose of acetaminophen. A two tablet or two capsule dose may still be prescribed, if appropriate. In that case, the total dose of acetaminophen would be 650 mg (the amount in two 325 mg dosage units). When making individual dosing determinations, health-care providers should always consider the amounts of both the acetaminophen and the opioid components in the prescription combination drug product.

In January 2011, the US FDA asked manufacturers of prescription combination drug products containing acetaminophen to limit the amount of acetaminophen to no more than 325 mg in each tablet or capsule by January 14, 2014. The US FDA requested this action to protect consumers from the risk of severe liver damage which can result from taking too much acetaminophen. This category of prescription drugs combines acetaminophen with another ingredient intended to treat pain (most often an opioid), and these products are commonly prescribed to consumers for pain, such as pain from acute injuries, post-operative pain, or pain following dental procedures. Acetaminophen is also widely used as an over-the-counter (OTC) pain and fever medication, and is often combined with other ingredients, such as cough and cold ingredients. The US FDA will address OTC acetaminophen products in another regulatory action. It is also notified that many consumers are often unaware that many products (both prescription and OTC) contain acetaminophen, making it easy to accidentally take too much.

(See WHO Pharmaceuticals Newsletter No.1, 2011 for the maximum amount limited to 325 mg per dosage unit and a boxed Warning will highlight the potential for severe liver failure in the USA).

References:

FDA Drug Safety Communication, US FDA 14 January 2014 (www.fda.gov).

Acipimox

Only to be used as additional or alternative treatment to reduce high triglyceride levels

Europe. The Co-ordination Group for Mutual Recognition and Decentralised Procedures – Human (CMDh) confirmed by majority that medicines containing acipimox (Olbetam® and generics) should have their marketing authorisations amended to ensure that they are used across the European Union (EU) only as an additional or alternative treatment in Fredrickson type IIb or type IV hyperlipoproteinaemia. These are conditions involving hypertriglyceridaemia with or without increased cholesterol. Acipimox-containing medicines should be used when changes in lifestyle, including diet and exercise, and treatment with other medicines are not adequate.

Health-care professionals are informed that, based on the available data, the indications for acipimox should be restricted to alternative or adjunct treatment in patients who have not responded adequately to other treatments such as statin or fibrate treatment. Patients receiving acipimox should have their treatment reviewed at their next regular appointment. The main role of acipimox is to prevent the non-cardiovascular complications of hypertriglyceridaemia and acipimox should not be used for the prevention of cardiovascular disease in the absence of convincing LDL-C or outcome data.

Prescribers are warned of the potential increased risk of myopathy when acipimox is

used in combination with a statin.

Reference:
Press release, EMA, 22 November 2013 (*www.ema.europa.eu*).

Capecitabine

Risk of severe skin reactions

Canada (1). Hoffmann-La Roche Limited (Roche), in consultation with Health Canada, informed health-care professionals that very rare cases of severe cutaneous reactions such as Stevens-Johnson syndrome (SJS) and Toxic Epidermal Necrolysis (TEN), in some cases with fatal outcome, have been reported during treatment with capecitabine (Xeloda®). It is advised that the drug should be immediately discontinued if signs and symptoms of SJS or TEN are present.

UK (2). The Medicines and Healthcare products Regulatory Agency (MHRA) announced that severe skin reactions such as SJS and TEN were reported during treatment with capecitabine. Some cases were fatal. The MHRA advised health-care professionals that capecitabine should be discontinued if a serious skin reaction occurs, and the reaction should be treated promptly.

Capecitabine is a first-line, adjuvant, or combination treatment for colon cancer, and for metastatic colorectal cancer, gastric cancer, or breast cancer.

Skin reactions associated with the use of capecitabine include palmar-plantar erythrodysaesthesia (hand-foot syndrome) and dermatitis, which occur very commonly (ie, >10% of patients). Rash, alopecia, erythema, and dry skin are common reactions. Furthermore, pruritus, localised exfoliation, skin hyperpigmentation, photosensitivity reactions, and radiation recall syndromes (severe skin reactions that can occur when chemotherapy agents are administered after radiotherapy) have also been seen with capecitabine.

Reference:
(1) Advisories, Warnings and Recalls, Health Canada, 3 December 2013 (*www.hc-sc.gc.ca*).
(2) Drug Safety Update, January 2013, Volume 7, issue 6, A4 MHRA, (*www.mhra.gov.uk*).

Clobazam

Risk of serious skin reactions

USA. The US FDA warned that clobazam (Onfi®) can cause rare but serious skin reactions Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) that can result in permanent harm and death. These skin reactions can occur at any time during clobazam treatment. However, the likelihood of skin reactions is greater during the first 8 weeks of treatment or when the drug is stopped and then re-started. All cases of SJS and TEN in the US FDA case series have resulted in hospitalization, one case resulted in blindness, and one case resulted in death. The clobazam drug label has been revised to add information about the risk for serious skin reactions to the Warnings and Precautions section and to the Medication Guide.

Clobazam is a benzodiazepine medication used in combination with other medicines to treat seizures associated with a severe form of epilepsy called Lennox-Gastaut Syndrome.

It is recommended that patients should be closely monitored for signs or symptoms of SJS/TEN, especially during the first 8 weeks of treatment or when re-introducing therapy. Health-care professionals should discontinue use and consider an alternate therapy at the first sign of rash, unless it is clearly not drug-related.

Patients are also recommended to seek immediate medical treatment if they develop a rash, blistering or peeling of the skin, sores in the mouth, or hives. Patients should not stop taking clobazam without first talking to their health-care professionals.

References:
FDA Drug Safety Communication, US FDA 3 December 2013 (*www.fda.gov*).

Duloxetine

Serotonin syndrome

Australia. The Therapeutic Goods Administration (TGA) reminded health-care professionals that, while serotonin syndrome most commonly occurs when serotonergic drugs are used in combination, it can be caused by a single drug. The TGA received 21 reports of serotonin syndrome in which duloxetine (Cymbalta® and generics) is the sole suspected drug.

Duloxetine is a serotonin and noradrenaline reuptake inhibitor indicated for the treatment of major depressive disorder, generalised anxiety disorder and diabetic peripheral neuropathic pain.

Serotonin syndrome is a known risk associated with duloxetine therapy and is listed as a precaution in the Product Information (PI).

Serotonin syndrome is characterised by:
- altered mental state, e.g. confusion and agitation
- autonomic dysfunction, e.g. tachycardia and sweating
- neuromuscular excitation, e.g. hyperreflexia, tremor.

Duloxetine should be used with caution with other serotonergic drugs, and concomitant treatment with monoamine oxidase inhibitors (MAOIs), including moclobemide, is contraindicated. Duloxetine should not be used within 14 days of discontinuing treatment with an MAOI, and at least five days should be allowed after stopping duloxetine before starting an MAOI. Similarly, as duloxetine is metabolised by both CYP1A2 and CYP2D6, it should not be used in combination with potent inhibitors of CYP1A2 (such as fluvoxamine). Treatment with duloxetine should be discontinued if signs or symptoms of serotonin syndrome are identified. Duloxetine should also not be used in patients with hepatic impairment, and use of a lower dose is recommended in patients with end-stage renal disease (creatinine clearance <30 mL/min).

Reference:
Medicines Safety Update Vol 4, No. 6, December 2013 (www.tga.gov.au).

Finasteride and dutasteride

Risk of high-grade prostate cancer

Australia. The TGA added new warnings regarding the risk of high-grade prostate cancer to the Product Information (PI) documents for the 5-alpha reductase inhibitors (5ARIs) finasteride and dutasteride. 5ARIs are a class of drug primarily used to treat symptomatic benign prostatic hyperplasia (BPH) in men. The two 5ARIs registered in Australia are finasteride (Proscar® and Propecia®) and dutasteride (Avodart® and Duodart® [in combination with tamsulosin]). Propecia is only indicated for the treatment of male pattern hair loss.

The TGA has reviewed a US Food and Drug Administration (FDA) assessment of two large trials that evaluated the use of finasteride or dutasteride daily versus placebo for the reduction in risk of prostate cancer. Both trials showed an increased incidence of high-grade prostate cancer. The TGA has since worked with the sponsors of finasteride and dutasteride to update the Australian PI documents to include a new precaution regarding the risk of patients developing high-grade prostate cancer.

The TGA informed health-care professionals that 5ARIs are not approved for the treatment of prostate cancer and no clinical benefit has yet been demonstrated in patients with prostate cancer treated with 5ARIs and recommended that, before making a decision to prescribe a 5ARI, the known risks should be weighed against the benefits of 5ARI therapy and discussed with the patient.

(See WHO Pharmaceuticals Newsletter No. 4, 2011 for increased risk of prostate cancer in the USA and No. 6, 2009 for finasteride's potential risk of male breast cancer in the UK).

Reference:
Medicines Safety Update Vol 4, No. 6, December 2013 (www.tga.gov.au).

Methylphenidate

Risk of long-lasting erections

USA. The US FDA warned that methylphenidate products (Concerta®, Daytrana®, Focalin®/Focalin® XR, Metadate™ CD/Metadate™ ER, Methylin®/Methylin® ER, Quillivant XR™, Ritalin®/Ritalin® LA/Ritalin-SR®) may in rare instances cause prolonged and sometimes painful erections known as priapism. Based on a recent review of methylphenidate products, the US FDA updated drug labels and patient Medication Guides to include information about the rare but serious risk of priapism. If not treated right away, priapism can lead to permanent damage to the penis.

Methylphenidate products are central nervous system (CNS) stimulants used to treat attention deficit hyperactivity disorder (ADHD).

Priapism can occur in males of any age and happens when blood in the penis becomes trapped, leading to an abnormally long-lasting and sometimes painful erection. According to the US FDA, another ADHD drug, atomoxetine (Strattera®), has also been associated with priapism in children, teens, and adults. Priapism appears to be more common in patients taking atomoxetine than in those taking methylphenidate products; however, because of limitations in available information, the US FDA does not know how often priapism occurs in patients taking either type of product.

It is recommended that health-care professionals should talk to male patients and their caregivers to make sure they know the signs and symptoms of priapism and stress the need for immediate medical treatment should it occur. Younger males, especially those who have not yet reached puberty, may not recognize the problem or may be embarrassed to tell anyone if it occurs. It is also recommended to encourage their patients to read the Medication Guide they receive with every filled prescription.

References:
FDA Drug Safety Communication, US FDA 17 December 2013 (*www.fda.gov*).

Ofatumumab

Screen for hepatitis B virus before treatment

UK (1). The MHRA advised that all patients should be screened for hepatitis B virus infection before starting treatment with ofatumumab (Arzerra®). Patients with active infection with this virus should not be treated with ofatumumab. Those with positive hepatitis B serology should be referred to a specialist in liver disease for consultation about monitoring and initiation of antiviral treatment. If reactivation of hepatitis B virus occurs, ofatumumab and any concomitant chemotherapy should be interrupted immediately, and appropriate treatment instituted

Ofatumumab is indicated for the treatment of chronic lymphocytic leukaemia in patients who are refractory to fludarabine and alemtuzumab. Ofatumumab is a monocolonal antibody that acts against CD20.

Canada (2). GSK, in consultation with Health Canada, informed health-care professionals of important new updates to the recommendations for screening, monitoring and management of Hepatitis B reactivation in patients treated with ofatumumab (ARZERRA™).

Ofatumumab is an anti-CD20 antibody that is authorized in Canada under a Notice of Compliance with conditions, for the treatment of patients with chronic lymphocytic leukemia (CLL) refractory to fludarabine and alemtuzumab.

Health-care professionals are advised that the use of anti-CD20 antibody therapies such as ofatumumab were shown to be associated with Hepatitis B virus reactivation in seropositive patients. Patients who have active Hepatitis B virus (HBV) infection should not be treated with the drug. All patients should be screened for HBV infection before starting treatment with the drug. In seropositive patients, consultation with a physician having expertise in liver disease is recommended. Patients should be monitored for clinical and laboratory signs of hepatitis or HBV reactivation during therapy and for several months after completion of treatment.

(See WHO Pharmaceuticals Newsletter No.6, 2013 for new boxed warning, recommendations to decrease risk of hepatitis B reactivation in the USA).

Reference:

(1) Drug Safety Update, January 2013, Volume 7, issue 6, A2 MHRA, (www.mhra.gov.uk).
(2) Advisories, Warnings and Recalls, Health Canada, 27 January 2013 (www.hc-sc.gc.ca).

Prasugrel

Association with increased risk of bleeding in patients treated in hospital for certain types of heart attacks

Canada (1). Eli Lilly Canada Inc. in collaboration with Health Canada informed health-care professionals of important safety information about prasugrel hydrochloride (Effint®), an antiplatelet agent indicated for the prevention of atherothrombotic events in patients with acute coronary syndromes. This information concerns the indication related to UA (unstable angina) or NSTEMI (non-ST-segment elevation myocardial infarction).

In UA/NSTEMI patients, when coronary angiography is performed within 48 hours after admission, the loading dose of prasugrel hydrochloride should generally be given at the time of percutaneous coronary intervention (PCI) in order to minimize the risk of bleeding.

It is also advised that UA/NSTEMI patients should generally be administered a 60 mg loading dose of prasugrel hydrochloride at the time of PCI, followed by a 10 mg maintenance dose.

UK (2). The MHRA advised health-care professionals that:

- Prasugrel is approved as a single 60 mg loading dose (followed by a maintenance dose recommended for up to 1 year); this remains unchanged
- Patients with unstable angina or NSTEMI, who undergo coronary angiography within 48 hours of admission, should be given a loading dose of 60 mg at the time of PCI only, to minimise bleeding risk
- Remember that a reduced maintenance dose of 5 mg once daily should be used (recommended for up to 1 year) if patients are age 75 years or older, or if their bodyweight is less than 60 kg

Prasugrel is a member of the thienopyridine class of medicines, and it inhibits platelet activation and aggregation. Prasugrel is indicated, in combination with aspirin, for the prevention of atherothrombotic events in patients with acute coronary syndrome undergoing primary or delayed percutaneous coronary intervention (PCI).

Reference:

(1) Advisories, Warnings and Recalls, Health Canada, 17 January 2013 (www.hc-sc.gc.ca).
(2) Drug Safety Update, January 2013, Volume 7, issue 6, A1 MHRA, (www.mhra.gov.uk).

Recombinant interferon-beta

Thrombotic microangiopathy

UK. The MHRA is investigating a cluster of reports of thrombotic microangiopathy with recombinant interferon-beta, which is used in the treatment of multiple sclerosis. Thrombotic microangiopathy is a very rare but serious condition characterised by occlusive microvascular thrombosis and secondary haemolysis, and it is a hallmark of haemolytic uraemic syndrome and thrombotic thrombocytopenic purpura. The MHRA received a total of 10 reports in the UK of thrombotic microangiopathy, haemolytic uraemic syndrome and/or thrombotic thrombocytopenic purpura.

Health-care professionals are advised to be vigilant for symptoms and signs that may be an early indication of this complication in patients receiving recombinant interferon-beta.

Reference:
Drug Safety Update, December 2013, Volume 7, issue 5, S3 MHRA, (*www.mhra.gov.uk*).

Regadenoson and adenosine

Rare but serious risk of heart attack and death

obstructions in the heart's arteries. Regadenoson and adenosine cause blood to flow preferentially to the healthier, unblocked or unobstructed arteries, which can reduce blood flow in the obstructed artery. In some cases, this reduced blood flow can lead to a heart attack, which can be fatal.

The Warnings & Precautions section of the regadenoson and adenosine labels previously contained information about the possible risk of heart attack and death with use of these drugs. However, recent reports of serious adverse events in the US FDA Adverse Event Reporting System (FAERS) database and the medical literature prompted approval changes to the drug labels to include updated recommendations for use.

It is recommended to screen all nuclear stress test candidates for their suitability to receive regadenoson or adenosine. Avoid using these drugs in patients with signs or symptoms of unstable angina or cardiovascular instability, as these patients may be at greater risk for serious cardiovascular adverse reactions. Cardiac resuscitation equipment and trained staff should be available before administering regadenoson or adenosine.

The US FDA approved changes to the drug labels to reflect these serious events and updated recommendations for

in all patients (not only those at risk of this infection) before starting treatment for all indications. A patient with positive serology for hepatitis B virus should be referred to a specialist in liver disease before starting treatment with rituximab. During treatment, these patients should be monitored and managed to prevent reactivation of the virus. Health-care professionals are also advised that patients with active hepatitis B disease should not be treated with rituximab.

Rituximab (MabThera®) is a treatment for adults with non-Hodgkin's lymphoma; chronic lymphocytic leukaemia; rheumatoid arthritis; or granulomatosis with polyangiitis and microscopic polyangiitis.

A recent review of all available data has shown that rituximab has been associated with reactivation of hepatitis B virus when used in the indications of cancer and rheumatoid arthritis.

(See WHO Pharmaceuticals Newsletter No.5, 2013 for HBV recurrence in patients and updates on screening and management in Canada and No.6, 2013 for new boxed warning, recommendations to decrease risk of HBV reactivation in the USA)

Reference:
Drug Safety Update, December 2013, Volume 7, issue 5, A1 MHRA, (*www.mhra.gov.uk*).