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 safety reports, advice, warnings and other updates from regulatory authorities across the world, including suspension and new restriction of the use of pioglitazone.

In this edition of the WHO Pharmaceuticals Newsletter, you will also find a summary of two training courses on pharmacovigilance hosted by the Pharmacy and Poisons Board, Kenya.

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Regulatory Matters

Safety of Medicines

Feature

Antipsychotic drugs

Risk of abnormal muscle movements and withdrawal symptoms in newborns

Canada. Health Canada informed health-care professionals and consumers that the prescribing information for the entire class of antipsychotic drugs is being updated. The updated labelling will contain safety information on the potential risk of abnormal muscle movements and withdrawal symptoms in newborns whose mothers were treated with these drugs during the third trimester of their pregnancy.

Antipsychotic drugs are used to treat symptoms of psychiatric disorders such as schizophrenia and bipolar disorder. Health Canada notified the Canadian manufacturers of antipsychotic drugs (typical and atypical) to update the Product Monographs to include this safety information.

Health Canada recommended that women taking an antipsychotic and who are pregnant or thinking of becoming pregnant should talk to their doctor about their treatment and that patients should not stop taking their medication without first speaking to a health-care practitioner, as abruptly stopping an antipsychotic drug can cause serious adverse events.

The abnormal muscle movements and withdrawal symptoms in newborns include agitation, abnormally increased or decreased muscle tone, tremor, sleepiness, severe difficulty breathing, and difficulty in feeding. These symptoms can vary in seriousness. In some newborns, the symptoms may go away within hours or days and not require specific treatment, while in others the symptoms may be more severe and require medical attention.

Reference:
Advisories, Warnings and Recalls, Health Canada, 15 June 2011 (*www.hc-sc.gc.ca*).

Belatacept

Increased risk of post-transplant lymphoproliferative disorder and progressive multifocal leukoencephalopathy

USA. The US Food and Drug Administration (US FDA) announced that Bristol-Myers Squibb (BMS) informed health-care professionals about the risk evaluation and mitigation strategy (REMS) that is required for belatacept (Nulojix®) to ensure that the benefits of belatacept outweigh the risks of post-transplant lymphoproliferative disorder (PTLD) and progressive multifocal leukoencephalopathy (PML), both of which can be fatal. Patients treated with belatacept are at an increased risk for developing PTLD, predominantly involving the central nervous system. PML has been reported in patients receiving belatacept at higher than recommended doses as part of an immunosuppressant regimen.

The US FDA may require a REMS from a manufacturer before approval or post approval to ensure that the benefits of a drug or biological product outweigh its risks. Belatacept is a selective T-cell co-stimulation blocker recently approved for prophylaxis of organ rejection in adult patients receiving a kidney transplant. Belatacept is to be used in combination with basiliximab induction, mycophenolate mofetil, and corticosteroids. Belatacept is indicated for use only in transplant patients who are Epstein-Barr virus (EBV) seropositive. Use in liver transplant patients is not recommended due to an increased risk of graft loss and death. Use of belatacept for the prophylaxis of organ rejection in other transplanted organs has not been established.

The US FDA recommended verifying the patient's EBV status before initiating therapy with belatacept.

Reference:
FDA Drug Safety Communication, US FDA 7 July 2011 (*www.fda.gov*).

Dexrazoxane

Restriction in Use

Europe. The European Medicines Agency (EMA) has recommended restricting the use of dexrazoxane to adult patients with advanced or metastatic breast cancer who have already received a certain amount of the anthracyclines doxorubicin and epirubicin to treat their cancer. The Agency's Committee for Medicinal Products for Human Use (CHMP) also recommended contraindicating the use of this medicine in children.

Dexrazoxane is currently indicated for use in patients with cancer to prevent long-term toxic effects on the heart caused by treatment with doxorubicin and epirubicin.

The review of dexrazoxane was initiated following concerns that it could be linked to an increased risk of acute myeloid leukaemia (AML) and myelodysplastic syndrome (MDS). This was based on studies in the United States

reporting cases of AML and MDS in children as well as on a small number of cases of AML reported in adult breast cancer patients receiving dexrazoxane.

Following review of all available data, the Committee concluded that there was evidence of serious harm in children and adolescents receiving dexrazoxane and that the benefits of the medicine do not outweigh the risks in this age group. The Committee therefore recommended contraindicating dexrazoxane in patients under the age of 18.

With respect to the use of dexrazoxane in adults, the Committee concluded that the benefits of dexrazoxane only outweigh the risks in adult patients with advanced or metastatic breast cancer who have already received a minimum cumulative dose of 300 mg/m^2 of doxorubicin or 540 mg/m^2 of epirubicin. It also recommended that the use of dexrazoxane when used with doxorubicin should be reduced from a dose ratio of 20:1 (20 parts dexrozaxone to 1 part doxorubicin) to a ratio of 10:1. The dose ratio of dexrazoxane to epirubicin remains unchanged at 10:1. When deciding to use dexrazoxane, prescribers should carefully weigh the possible benefits in relation to the protection of the heart against the short- and long-term risks, particularly the risk of AML and MDS.

Reference:
Press release, EMA, 23 June 2011 (*www.ema.europa.eu*).

Epoetin alfa and Darbepoetin alfa

Modified dosing recommendations

USA. The US FDA notified health-care professionals of new, modified recommendations for more conservative dosing of erythropoiesis-stimulating agents (ESAs) which include epoetin alfa and darbepoetin alfa in patients with chronic kidney disease (CKD) to improve the safe use of these drugs.

ESAs treat certain types of anaemia by stimulating the bone marrow to produce red blood cells and by decreasing the need for blood transfusions. The manufacturer has revised the Boxed Warning, Warnings and Precautions, and Dosage and Administration sections of the labels for the ESAs to include this new information.

The US FDA has made these recommendations because of data showing increased risks of cardiovascular events with ESAs in this patient population. The new dosing recommendations are based on clinical trials showing that using ESAs to target a haemoglobin level of greater than 11 g/dl in patients with CKD provides no additional benefit than lower target levels, and increases the risk of experiencing serious adverse cardiovascular events, such as heart attack or stroke.

The US FDA recommended that health-care professionals should weigh the possible benefits of using ESAs to decrease the need for red blood cell transfusions in CKD patients against the increased risks for serious cardiovascular events, and should inform their patients of the current understanding of potential risks and benefits. Therapy should be individualized to the patient and the lowest possible ESA dose given to reduce the need for transfusions.

(See WHO Pharmaceuticals Newsletter No. 5 and 6, 2008 for the review of the safety of epoetin alfa in the USA and reports in WHO Global ICSR database.)

Reference:
FDA Drug Safety Communication, US FDA 24 June 2011 (*www.fda.gov*).

Finasteride and Dutasteride

Increased risk of prostate cancer

USA. The US FDA notified health-care professionals that the Warnings and Precautions section of the labels for the 5-alpha reductase inhibitor (5-ARI) class of drugs which include finasteride and dutasteride has been revised to include new safety information about the increased risk of being diagnosed with a more serious form of prostate cancer (high-grade prostate cancer).

These drugs are marketed under the brand-names Proscar®, Propecia®, Avodart®, and Jalyn® in the USA. Proscar, Avodart, and Jalyn are approved to improve symptoms of an enlarged prostate gland (benign prostatic hyperplasia or BPH). Proscar and Avodart are also approved to reduce the risk of urinary retention or surgery related to an enlarged prostate. Propecia is approved to treat male pattern hair loss.

The new safety information is based on the US FDA's review of two large, randomized controlled trials–the Prostate Cancer Prevention Trial (PCPT) and the Reduction by Dutasteride of Prostate Cancer Events (REDUCE) trial.

The US FDA recommended that prior to initiating therapy with 5-ARIs, there should be appropriate evaluation to rule out other urological conditions,

including prostate cancer, that might mimic benign prostatic hyperplasia (BPH).

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

Reference:
FDA Drug Safety Communication, US FDA 9 June 2011 (*www.fda.gov*).

H1N1 influenza vaccine (Pandemrix)

Restricting use of Pandemrix

Europe. The EMA announced that the CHMP finalized its review of Pandemrix and narcolepsy and recommended that in persons under 20 years of age Pandemrix may only be used if the recommended seasonal trivalent influenza vaccine is not available and if immunization against H1N1 is still needed (e.g. in persons at risk of the complications of infection). The CHMP confirmed that overall the benefit-risk balance of Pandemrix remains positive.

The CHMP considered all available data on the possible association between Pandemrix and narcolepsy and the impact on the overall benefit-risk balance of Pandemrix. These included the results of epidemiological studies carried out in Finland and Sweden, analysis of safety surveillance data performed in several Member States and case reports from across the European Union (EU). They also included the preliminary results of an epidemiological study of narcolepsy and pandemic vaccines in eight EU Member States, coordinated by the European Centre for Disease Prevention and Control (ECDC) through a network of research and public health institutions (VAESCO).

The CHMP also took advice from a specially convened meeting of experts in fields such as paediatric neurology, vaccinology, immunology, sleep disorders, infectious diseases, epidemiology, as well as experts from Health Canada, WHO and the ECDC, to consider the latest available data regarding the possible link between Pandemrix and narcolepsy.

The CHMP noted that similar epidemiological studies have not been completed in other countries. The preliminary results of the VAESCO study confirmed the signal in Finland. Results are still preliminary and do not allow conclusions in other countries (where vaccination coverage with Pandemrix was lower), but the final results of the VAESCO study are still awaited. The CHMP stressed that further research is necessary.

The marketing authorization holder for Pandemrix, GlaxoSmithKline, is carrying out a retrospective cohort study in Canada, where an equivalent H1N1 vaccine (Arepanrix) was widely used. The company is required to carry out non-clinical and clinical studies in order to further explore the association between Pandemrix vaccination and narcolepsy.

(See WHO Pharmaceuticals Newsletter No.1, 2011 for the study on the suspected link between narcolepsy and Pandemrix in Europe.)

Reference:
Press release, EMA, 21 July 2011 (*www.ema.europa.eu*).

Leflunomide

Wash-out procedure added to the data sheet

New Zealand. New Zealand Medicines and Medical Devices Safety Authority (Medsafe) advised that prescribers are reminded that if serious adverse reactions occur, leflunomide must be stopped and a cholestyramine or charcoal wash-out procedure initiated immediately. In addition, rheumatology advice should be sought for all patients experiencing serious adverse reactions to leflunomide. Medsafe also encouraged prescribers to familiarize themselves with the prescribing information for leflunomide.

Leflunomide is a disease modifying anti-rheumatic drug indicated for the treatment of rheumatoid arthritis and active psoriatic arthritis. Leflunomide can cause serious and potentially life-threatening adverse reactions involving the liver, blood, lungs and skin. Due to its immunosuppressant effects leflunomide can also cause life-threatening infections, particularly when given in combination with other immunosuppressant medicines. As leflunomide has a very long half-life (usually 1-4 weeks), adverse reactions can occur or persist long after leflunomide is discontinued.

According to Medsafe, safety information has recently been added to the data sheet to include the following:

• Side-effects may occur more commonly if leflunomide is given concomitantly with other hepatotoxic or haematotoxic medicines. Monitoring guidelines contained in the leflunomide data sheet should be carefully followed.

• Interstitial pneumonitis may occur more frequently with concomitant use of methotrexate.

• A wash-out procedure should be used for all serious adverse reactions. This information is

included in a new subsection of the data sheet "Washout procedure for severe adverse reactions".

(See WHO Pharmaceuticals Newsletter No. 4, 2010 for new boxed warning for severe liver injury in the USA and reports in WHO Global ICSR database.)

Reference:
Prescriber Update Vol. 32 No. 2, June 2011 (*www.medsafe.govt.nz*).

Linezolid

Serious CNS reactions possible in patients taking certain psychiatric medications

USA. The US FDA announced that the Agency has received reports of serious central nervous system (CNS) reactions when the antibacterial drug linezolid (Zyvox®) is given to patients taking psychiatric medications that work through the serotonin system of the brain (serotonergic psychiatric medications). Safety information about this potential drug interaction and important drug usage recommendations for emergency and non-emergency situations are being added to the drug labels for serotonergic psychiatric medications and linezolid.

Linezolid is used to treat infections, including pneumonia, infections of the skin, and infections caused by a resistant bacterium (Enterococcus faecium). It is a reversible monoamine oxidase inhibitor (MAOI). Although the exact mechanism of this drug interaction is unknown, linezolid inhibits the action of monoamine oxidase A. It is believed that when linezolid is given to patients taking serotonergic psychiatric medications, high levels of serotonin can build up in the brain, causing toxicity. This is referred to as Serotonin Syndrome — signs and symptoms include mental changes (confusion, hyperactivity, memory problems), muscle twitching, excessive sweating, shivering or shaking, diarrhea, trouble with coordination and/or fever.

The US FDA recommended that linezolid should generally not be given to patients taking serotonergic drugs; however patients should not stop taking their serotonergic psychiatric medicine without first talking to a health-care professional.

Reference:
FDA Drug Safety Communication, US FDA 26 July 2011 (*www.fda.gov*).

Methylene blue

Serious CNS reactions possible in patients Taking certain psychiatric medications

USA. The US FDA announced that the Agency has received reports of CNS reactions when the drug methylene blue is given to patients taking psychiatric medications that work through the serotonin system of the brain (serotonergic psychiatric medications). Safety information about this potential drug interaction and important drug usage recommendations for emergency and non-emergency situations are being added to the drug labels for serotonergic psychiatric medications.

Methylene blue is used to treat methemoglobinemia, vasoplegic syndrome, ifosfamide-induced encephalopathy, and cyanide poisoning. It is also used as a dye in therapeutic and diagnostic applications. Methylene blue is a potent, reversible MAOI. It is believed that when methylene blue is given to patients taking serotonergic psychiatric medications, high levels of serotonin can build up in the brain, causing toxicity (Serotonin Syndrome).

The US FDA recommended that methylene blue should generally not be given to patients taking serotonergic drugs. However, there are some conditions that may be life-threatening or require urgent treatment with methylene blue such as when it is used in the emergency treatment of methemoglobinemia, ifosfamide-induced encephalopathy, or cyanide poisoning. The US FDA also recommended that patients should not stop taking their serotonergic psychiatric medicine without first talking to a health-care professional.

Reference:
FDA Drug Safety Communication, US FDA 26 July 2011 (*www.fda.gov*).

Metoclopramide

Stronger warnings on risk of abnormal muscle movements

Canada. Health Canada informed health professionals and consumers that the labelling information for the drug metoclopramide is updated to include stronger warnings on the risk of a movement disorder known as "tardive dyskinesia." The risk increases with longer treatment and is higher in the elderly, especially elderly women.

Tardive dyskinesia usually appears as involuntary movements of the tongue, face, mouth or jaw. These movements can include lip smacking, chewing, or puckering, or sticking out of the tongue. Sometimes, movements can include the torso or limbs, such as leg shaking. There are no known treatments for tardive dyskinesia once it has become established.

Tardive dyskinesia is a known side-effect associated with metoclopramide. The current prescribing information contains information on this risk. Health Canada is working with the Canadian manufacturers to include stronger, more detailed warnings in the drug labelling that contain the following information:

• Tardive dyskinesia may develop in patients treated with metoclopramide. The elderly, especially elderly women, appear to be at increased risk.

• The risk appears to increase with treatment length and the total amount of drug taken.

• Tardive dyskinesia is more likely to be irreversible with long-term treatment (over 12 weeks).

• Less frequently, tardive dyskinesia can develop with short term treatment at low

Metoclopramide is most commonly used to treat digestive problems associated with a stomach that empties too slowly. Health Canada reminded health-care professionals that metoclopramide is not authorized in Canada for the following: treatment of hiccups, diabetic gastroparesis (partial paralysis of the stomach), nausea and vomiting in pregnancy, or for symptoms of bloating or constipation associated with eating disorders.

(See WHO Pharmaceuticals Newsletter No. 2, 2009 for warning against chronic use in the USA and reports in WHO Global ICSR database.)

Reference:
Advisories, Warnings and Recalls, Health Canada, 20 July 2011 (www.hc-sc.gc.ca).

Nimesulide

Use to be restricted to treatment of acute pain and primary dysmenorrhoea

Europe. The CHMP has concluded that the benefits of systemic nimesulide-containing medicines continue to outweigh their risks in the treatment of patients with acute pain and primary dysmenorrhoea. However,

request of the Committee in 2007, all available reports on adverse drug reactions and data from the published literature. The Committee noted that, in treatment of acute pain, nimesulide is as effective as other NSAID pain killers, such as diclofenac, ibuprofen and naproxen. In terms of safety, the CHMP noted that nimesulide has the same risk of gastrointestinal toxicity as other NSAIDs.

The CHMP concluded that nimesulide was associated with an increased risk of liver toxicity compared with other anti-inflammatory treatments. The Committee had previously imposed several restrictions on the use of systemic nimesulide in order to reduce risks of liver injury. Having reviewed all available data, the CHMP is now recommending, as a further restriction, that systemic nimesulide should no longer be used for the treatment of painful osteoarthritis. The Committee considered that the use of systemic nimesulide for the treatment of this chronic condition, would increase the risk of the medicines being used for long-term treatment, with a consequent increase in the risk of liver injury.

(See WHO Pharmaceuticals Newsletter No. 3, 5 and 6, 2007 for review and regulatory outcome in Ireland and EU.)