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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This Newsletter is also available on our Internet website:
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No. 6, 2012

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. We thank you for your interest in this publication and wish you a healthy and fulfilling year in 2013.

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Regulatory Matters

Safety of medicines

Signal

Agomelatine

Risk of dose-related hepatotoxicity and liver failure

UK. The Medicines and Healthcare products Regulatory Agency (MHRA) announced that there have been several serious cases of hepatotoxicity reported with agomelatine (Valdoxan®, Thymanax®). These include six reports worldwide of hepatic failure. The agency advised health-care professionals that the existing recommendations to perform liver function tests in all patients receiving agomelatine at treatment initiation and during treatment have been extended to include testing when the dose is increased. Agomelatine should be immediately discontinued if patients present with symptoms or signs of potential liver injury, or if an increase in serum transaminases in liver function tests exceeds 3 times the upper limit of normal. It is also recommended that patients should be informed of the symptoms of potential liver injury and advised to stop taking agomelatine immediately and seek urgent medical advice if these symptoms appear.

Agomelatine is an antidepressant indicated for the treatment of major depressive episodes in adults. Agomelatine is a melatonin MT1 and MT2 receptor agonist, and antagonist at the serotonin 5-HT_{2C} receptor, thereby increasing levels of dopamine and noradrenaline in areas of the brain involved in mood control.

Reference:
Drug Safety Update, October 2012, Volume 6, issue 3, A1 MHRA, (*www.mhra.gov.uk*).

Denosumab

Fatal cases of severe symptomatic hypocalcaemia

UK. The MHRA reported that cases of severe symptomatic hypocalcaemia have occurred in patients receiving denosumab 120 mg (Xgeva®) or 60 mg (Prolia®). Some of these cases were fatal in those receiving the 120 mg dose.

The MHRA advised health-care professionals that pre-existing hypocalcaemia must be corrected prior to initiating denosumab, and supplementation of calcium and vitamin D is required in all patients receiving the 120 mg dose unless hypercalcaemia is present. Although hypocalcaemia most commonly occurs within the first 6 months of treatment, it may occur at any time.

Hypocalcaemia is a known risk with denosumab use, especially in patients with severe renal impairment (creatinine clearance <30 mL/min; estimated glomerular filtration rate [eGFR] 15 – 29 mL/min/1.73m^2) or receiving dialysis. Severe symptomatic hypocalcaemia, including three fatal cases, has been reported in patients receiving denosumab 120 mg. Severe symptomatic hypocalcaemia has also been reported in patients at increased risk of hypocalcemia receiving denosumab 60 mg.

Signs and symptoms of hypocalcaemia include altered mental status, tetany, seizures and QTc prolongation. Hypocalcaemia with denosumab most commonly occurs within the first 6 months of dosing, but it can occur at any time during treatment

Periodic monitoring of calcium levels (at the discretion of the prescriber) is recommended after use of denosumab in patients predisposed to hypocalcaemia, including those with severe renal impairment. In patients receiving 120 mg denosumab, supplementation of calcium and vitamin D is required unless hypercalcaemia is present; if hypocalcaemia occurs, additional calcium supplementation may be necessary.

Reference:
Drug Safety Update, October 2012, Volume 6, issue 3, A3 MHRA, (*www.mhra.gov.uk*).

Denosumab

Association with the risk of atypical femoral fractures

Canada. AMGEN Canada Inc., in consultation with Health Canada, informed health-care providers of new important safety information regarding the risk of atypical femoral fractures associated with denosumab (Prolia®) treatment. According to the manufacturer, there have been no confirmed Canadian cases of atypical femoral fractures associated with denosumab to date. Amgen proactively evaluated the potential for atypical femoral fractures in patients treated with the drug in clinical trials and the post marketing setting.

Cases of atypical femoral fracture have been confirmed in patients receiving denosumab participating in the on-going open label extension study of the pivotal phase 3 fracture trial in postmenopausal osteoporosis (FREEDOM). Events of atypical femoral fracture have occurred very rarely (<1/10,000) based on 31,266 subject years of exposure to denosumab in bone loss studies.

It is recommended that, during denosumab treatment, health-care professionals should advise the patients to report new or unusual thigh, hip, or groin pain. Patients presenting

with such symptoms should be evaluated for an incomplete femoral fracture, and the contralateral femur should also be examined.

The Warnings and Precautions section of the Product monograph was updated to reflect this new information on atypical femoral fractures.

Reference:
Advisories, Warnings and Recalls, Health Canada, 16 November 2012 (*www.hc-sc.gc.ca*).

Intravenous 0.18% saline/4% glucose solution ('hypotonic saline') in children

Contraindicated in children except under expert medical supervision in paediatric specialist settings

UK (1). The MHRA announced that four children have died of cerebral oedema caused by very low levels of serum sodium after receiving intravenous hypotonic saline (0.18% saline/4% glucose solution) in hospital. This solution is now contraindicated in children except under expert medical supervision in paediatric specialist settings – such as renal, cardiac, liver, high dependency and intensive care units.

The MHRA also advised health-care professionals to remove 0.18% saline/4% glucose intravenous infusions from stock and general use in areas that treat children and ensure that suitable alternatives are available (in line with local guidelines) and to restrict availability of 0.18% saline/4% glucose intravenous infusions to critical care and specialist wards. If hypotonic intravenous fluids do need to be prescribed to children (according to the strict conditions above), the child's individual clinical needs and possibility of increased anti-diuretic hormone secretion should be taken into account – fluid balance, plasma and urinary electrolyte concentrations must be carefully monitored during treatment.

Acute symptomatic hyponatraemic encephalopathy is a medical emergency. Health-care professionals should therefore be aware of and take prompt action if children receiving hypotonic intravenous fluids develop the signs and symptoms of hyponatraemia (headache, nausea, seizures, lethargy, coma, cerebral oedema).

Following the restart of a public inquiry primarily into the deaths of three children in the UK who died of cerebral oedema secondary to hyponatraemia after administration of intravenous hypotonic saline, the Commission on Human Medicines (CHM) has recently reviewed all data on the benefits and risks of this solution when used in children.

There have been over 50 reported permanent neurological injuries or deaths in children worldwide as a result of iatrogenic hyponatraemia associated with the use of hypotonic intravenous fluids, often in previously healthy children undergoing routine elective surgery. In addition, several published studies and reviews have demonstrated hyponatraemia after administration of hypotonic intravenous fluids such as 0.18% saline/4% glucose.

On the basis of the evidence from the review, the CHM concluded that the use of 0.18% saline/4% glucose should be contraindicated in all but a limited group of children treated by experts in paediatric specialist settings, such as renal, cardiac, liver, high dependency, and intensive care units.

Egypt (2). The Pharmacovigilance Committee-Central Administration for Pharmaceutical Affairs (CAPA) decided to contraindicate the use of Intravenous (I.V.) solution containing 0.18% NaCl in children aged 16 years or less, except under expert medical supervision in paediatric specialist settings such as kidney, heart, liver, high-dependency and intensive care units.

In addition, the Pharmacovigilance Committee also requested that all Marketing Authorization Holders of I.V. solution containing 0.18% NaCl in Egypt to distribute "Dear Healthcare Professional Communication (DHPC)" to HealthCare settings to where your product is distributed to inform them with the new safety information.

Reference:
(1) Drug Safety Update, October 2012, Volume 6, issue 3, A2 MHRA, (*www.mhra.gov.uk*).
(2) Newsletter of the Egyptian Pharmaceutical Vigilance center, No. 35, Volume 3 December 2012.

Ondansetron

Dose restriction for intravenous use due to dose-dependent QT interval prolongation

Canada. GlaxoSmithKline Inc., in consultation with Health Canada, informed of new information regarding the risk of electrocardiographic QT interval prolongation associated with ondansetron (ZOFRAN®). A recently completed study identified a dose-dependent prolongation of the corrected QT interval (QTc) among healthy subjects treated with ondansetron. QTc interval prolongation can lead to Torsade de Pointes (TdP), a

potentially life-threatening heart rhythm abnormality.

Recommendations based on this new study are as follows:

- The new maximum recommended single intravenous (IV) dose is 16 mg infused over 15 minutes.
- The 32 mg IV dose and the 8 mg IV dose followed by a 1 mg/hour continuous infusion are no longer recommended and should not be used.
- Avoid ondansetron in patients with congenital long QT syndrome. Use caution if administering ondansetron to patients with other risk factors for QT interval prolongation, such as electrolyte abnormalities, congestive heart failure, bradyarrhythmias or use of other medicines that can lead to either QT prolongation or electrolyte abnormalities.
- Hypokalemia, hypomagnesemia, and hypocalcemia should be corrected prior to ondansetron administration.

Physicians are recommended to assess their patients for risk factors for QT interval prolongation or TdP before prescribing ondansetron. For adults treated with intravenous ondansetron prior to chemotherapy, the usual dose is 8 mg infused over 15 minutes at least 30 minutes prior to chemotherapy. It is recommended that the drug should not be administered more rapidly than recommended as more rapid infusion can lead to greater QTc prolongation.

It is also recommended that patients should be advised to contact their health-care professional if they experience signs or symptoms of an abnormal heart rate or rhythm while taking ondansetron (e.g., dizziness, palpitations, syncope).

There are no changes to recommended oral dosing in adults. There are no changes to recommended oral or intravenous dosing in children.

Reference:
Advisories, Warnings and Recalls, Health Canada, 3 October 2012 (www.hc-sc.gc.ca).

Proton Pump Inhibitors and Methotrexate

Interaction of proton pump inhibitors with methotrexate

Canada. Health Canada informed that the labelling for methotrexate and Proton Pump Inhibitors (PPIs) is being updated to include information on a potential interaction between these products. The new information will be in the "Warnings and Precautions" section of the methotrexate and the PPIs labelling. The use of high-dose methotrexate and of PPIs at the same time by patients may increase the amount of methotrexate in the blood leading to side effects. The possible risks to health include kidney failure, low red blood cell count, inflammation of the digestive tract, irregular heartbeat, muscle pain, infections, and diarrhea.

While a definite association between PPI use and an increase in methotrexate has not been confirmed, there have been a number of studies suggesting a possible interaction between PPIs and methotrexate. The potential for an increased risk of methotrexate side effects is very likely, which is why Health Canada informed this change in labelling. Health Canada will continue to evaluate the scientific evidence as it emerges and take appropriate action as needed.

It is recommended that patients should not stop taking their medication unless they have been advised to do so by their health-care professional. Patients using PPIs and methotrexate should consult with their doctor if they have any concerns about their health or these products.

Health-care practitioners are reminded that PPIs, in general, should be prescribed at the lowest dose and for the shortest duration of therapy appropriate to the condition being treated. As noted in the drug labels, a temporary withdrawal of the PPI may be considered by the health-care practitioner in some patients receiving treatments with high-dose methotrexate.

(See WHO Pharmaceuticals Newsletter No. 2, 2010 for updates on warning about interaction between clopidogrel and proton pump inhibitors in Europe and New Zealand and No. 3, 2010 for updated advice on possible interactions in UK).

Reference:
Advisories, Warnings and Recalls, Health Canada, 19 October 2012 (revised 24 October, 2012) (www.hc-sc.gc.ca).

Dabigatran etexilate mesylate

Safety review of post-market reports of serious bleeding events

USA. The U.S. Food and Drug Administration (US FDA) evaluated new information about the risk of serious bleeding associated with use of the anticoagulants dabigatran (Pradaxa®) and warfarin (Coumadin®, Jantoven®, and generics). This assessment was done using insurance claims and administrative data from the US FDA's Mini-Sentinel pilot of the Sentinel Initiative. The results of this assessment indicate that bleeding rates associated with new use of dabigatran do not appear to be higher than bleeding rates associated with new use of warfarin, which is consistent with observations from the large clinical trial used to approve Pradaxa®. The US FDA is continuing to evaluate multiple sources of data in the ongoing safety review of this issue. The US FDA has not changed its recommendations regarding the drug.

(See WHO Pharmaceuticals Newsletters No. 1, 2012 for safety review of post-market reports of serious bleeding events in the USA, Australia and New Zealand; Risk of serious haemorrhage, need for renal function testing in UK, No.3, 2012 for updated labelling regarding renal function assessment and use in patients with severe valvular disease or prosthetic heart valves in Canada and Saudi Arabia and No.4, 2012 for modifications to product information for clearer guidance in EU).

Reference:
FDA Drug Safety Communication, US FDA 2 November 2012 (*www.fda.gov*).

Human papillomavirus vaccine (Cervarix)

Cervarix: safety review shows balance of risks and benefits remains clearly positive

UK. The MHRA announced that a safety review conducted at the end of its routine use during the on-going human papillomavirus (HPV) immunisation programme found that no new risks have been identified for HPV vaccine Cervarix®, and that the balance of its risks and benefits remains clearly positive. Cervarix® was replaced in the programme by the HPV vaccine Gardasil® from September 2012. Since September 2008 the human papillomavirus (HPV) vaccine Cervarix® has been used extensively in the UK routine HPV immunisation programme to prevent cervical cancer.

The MHRA previously reported on the safety of the vaccine following the first and second year of use and the agency conducted a further safety review of the totality of the UK experience with Cervarix® up to the end of July 2012. No new safety concerns were identified and the number and nature of adverse reaction (ADR) reports received was as expected after administration of at least 6 million doses of the vaccine in the UK.

Before Cervarix® was first used the MHRA anticipated that a range of medical conditions naturally prevalent in the adolescent female population would occur in temporal association with vaccination and might be reported as suspect side effects. Statistical methods were therefore put in place to rapidly assess whether such reports were consistent with chance, or whether they could be new side effects of the vaccine. One such condition was chronic fatigue syndrome (CFS) – the level of reporting for which was found to be well within the expected background incidence rate. An ecological study and a self-controlled case series study using the Clinical Practice Research Datalink (CPRD) also did not find an increased risk of fatigue syndromes with Cervarix®.

Reference:
Drug Safety Update, November 2012, Volume 6, issue 4, H2 MHRA, (*www.mhra.gov.uk*).

Non-steroidal anti-inflammatory drugs (NSAIDs)

Pharmacovigilance Risk Assessment Committee to consider need for updated treatment advice for diclofenac in follow-on review

Europe. The European Medicines Agency (EMA) finalised a review of recently published information on the cardiovascular safety of non-steroidal anti-inflammatory drugs (NSAIDs). The Agency's Committee for Medicinal Products for Human Use (CHMP) concluded that evidence from newly available published data sources, including meta-analysis of clinical trials and observational studies, and the results of a European Union-funded independent research project, the 'safety of non-steroidal anti-inflammatory drugs' (SOS) project, on the cardiovascular safety of this class of medicines confirm findings from previous reviews, conducted in 2005 and 2006.

Most of the data related to the three most widely used NSAIDs – diclofenac, ibuprofen and naproxen. In relation to naproxen and ibuprofen, the CHMP was of the opinion that the current treatment advice adequately reflects the

knowledge regarding the safety and efficacy of these medicines.

For diclofenac, the latest evidence appears to show a consistent but small increase in the risk of cardiovascular side effects for diclofenac compared with other NSAIDs, similar to the risks of COX-2 inhibitors, another class of painkillers. As a follow-on to this review, the Agency's new Pharmacovigilance Risk Assessment Committee (PRAC) will now assess all available data on diclofenac (both published and unpublished) to consider the need for updated treatment advice.

Reference:
Press release, EMA, 19 October 2012 (*www.ema.europa.eu*).

Over-The-Counter Eye Drops and Nasal Sprays

Serious adverse events from accidental ingestion by children

USA. The US FDA warned health-care professionals and the public that accidental ingestion by children of over-the-counter eye drops used to relieve redness and nasal decongestant sprays can result in serious and life-threatening adverse events. The eye drops and nasal sprays that have been involved in the cases of accidental ingestion contain the active ingredients coma have occurred. Ingestion of only a small amount (1-2 mL; for reference, there are 5 mL in a teaspoon) of the eye drops or nasal spray can lead to serious adverse events in young children.

Most of these redness-relief eye drops and nasal decongestant sprays currently do not come packaged with child-resistant closures, so children can accidentally ingest the drug if the bottles are within easy reach. These products are sold under various brand names, as generics, and as store brands.

The US FDA recommended that consumers should store these products out of reach of children at all times. It is also recommended to call local poison control center immediately if a child accidentally swallows OTC redness-relief eye drops or nasal decongestant spray.

Reference:
FDA Drug Safety Communication, US FDA 25 October 2012 (*www.fda.gov*).

Simvastatin

Evidence supporting recent advice on dose limitations with concomitant amlodipine or diltiazem

UK. In August 2012 the MHRA published advice that simvastatin is contraindicated with concomitant use of certain result from such drug interactions.

Following further consideration by the Pharmacovigilance Expert Advisory Group of the Commission on Human Medicines, the MHRA published an article summarises the evidence underlying the new advice that the maximum recommended dose for simvastatin in conjunction with amlodipine and diltiazem is now 20 mg/day. The prescribed doses of amlodipine and diltiazem need not be changed.

In summary, the available evidence supports the recommendation that the maximum daily dose of simvastatin should not exceed 20 mg when co-administered with amlodipine or diltiazem:

- concomitant use of either amlodipine or diltiazem increases the exposure to simvastatin through CYP3A4 interactions
- the incidence of myopathy is increased with higher doses of simvastatin when co-administered with amlodipine or diltiazem, compared to the absence of amlodipine or diltiazem, or lower doses of simvastatin
- approximately 75% of the LDL-lowering effect is apparent at lower doses of simvastatin and only an additional