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: http://www.who.int/medicines

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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.

The feature article in this issue brings you the recommendations from the Thirty-fifth Annual Meeting of Representatives of National Pharmacovigilance Centres participating in the WHO Programme for International Drug Monitoring, in Brazil, 11-14 November 2012.

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Botulinum Toxin

New labelling information for all products

Canada. Health Canada requested all manufacturers of botulinum toxin products currently available on the Canadian market revise their product labels to reflect that each product has its own individual potency and as such is not interchangeable with other botulinum products.This revision is to help prevent medication errors with the use of these products.

The labelling changes are due to a risk evaluation of the active ingredients (Clostridium botulinum toxin type A and type B) within these products. Botulinum toxins are produced by different manufacturing processes, are obtained by different techniques and are derived from different Clostridium strains. As a result of these differences, these products cannot be interchanged as these changes can cause unexpected side-effects.

Health Canada advised health-care professionals that the established drug names of the botulinum products have not been changed yet to emphasize the differing dose-to-potency ratios of these products. Manufacturers will have one year to comply with the labelling change requests.

Reference:
Advisories, Warnings and Recalls, Health Canada, 21 January 2013 (*www.hc-sc.gc.ca*).

Dabigatran etexilate mesylate

Contraindication in patients with mechanical prosthetic heart valves

USA (1). The U.S. Food and Drug Administration (FDA) advised health-care professionals and the public that dabigatran etexilate mesylate (Pradaxa®) should not be used to prevent stroke or blood clots (major thromboembolic events) in patients with mechanical heart valves, also known as mechanical prosthetic heart valves. A clinical trial in Europe (the RE-ALIGN trial) was recently stopped because dabigatran users of the drug were more likely to experience strokes, heart attacks, and blood clots forming on the mechanical heart valves than were users of the anticoagulant warfarin. There was also more bleeding after valve surgery in the dabigatran etexilate mesylate users than in the warfarin users.

Dabigatran etexilate mesylate is not approved for patients with atrial fibrillation caused by heart valve problems by the US FDA. The US FDA is requiring a contraindication of the drug in patients with mechanical heart valves.

It is recommended that health-care professionals should promptly transition any patient with a mechanical heart valve who is taking dabigatran etexilate mesylate to another medication. The use of dabigatran etexilate mesylate in patients with another type of valve replacement made of natural biological tissue, known as a bioprosthetic valves, has not been evaluated and cannot be recommended. Patients with all types of prosthetic heart valve replacements taking dabigatran etexilate mesylate should talk to their health-care professional as soon as possible to determine the most appropriate anticoagulation treatment. Patients should not stop taking anticoagulant medications without guidance from their health-care professional; stopping dabigatran etexilate mesylate or other anticoagulants suddenly can increase the risk of blood clots and stroke.

Canada (2). Boehringer Ingelheim (Canada) Ltd., in consultation with Health Canada, has announced that dabigatran etexilate (Pradaxa™ and Pradax®) Product Monograph will be revised to include a new contraindication for use in patients with prosthetic heart valves requiring anticoagulant treatment due to their valvular status.

(See WHO Pharmaceuticals Newsletters Nos. 1, 3, 4 and 6, 2012 for previous related announcements).

References:
(1) FDA Drug Safety Communication, US FDA 19 December 2012 (*www.fda.gov*).
(2) Advisories, Warnings and Recalls, Health Canada, 21 December 2012 (*www.hc-sc.gc.ca*).

Domperidone

Serious ventricular arrhythmias and sudden cardiac death

Australia. The Therapeutic Goods Administration (TGA) advised health-care professionals that domperidone (Motilium®) should be initiated at the lowest possible dose in adults. Recent epidemiological studies have shown that the use of domperidone may be associated with an increased risk of serious ventricular arrhythmias or sudden cardiac death, particularly in patients taking daily doses greater than 30 mg, and in patients older than 60 years of age.

Patients should be advised to stop taking domperidone and seek immediate medical attention if they experience signs or symptoms of an abnormal heart rate or rhythm while taking domperidone. These include dizziness, palpitations, syncope or seizures.

Health-care professionals are advised that:

- Domperidone is contraindicated with ketaconazole, erythromycin or other potent CYP3A4 inhibitors which prolong QTc interval such as fluconazole, voriconazole, clarithromycin and amiodarone
- Domperidone should be used with caution and at the lowest effective dose in at-risk patients such as those:
  - with existing prolongation of cardiac conduction intervals (particularly the QT interval)
  - using potent CYP3A4 inhibitors which may increase plasma levels of domperidone such as itraconazole, amprenavir, atazanavir, fosamprenavir, indinavir, nelfinavir, ritonavir, saquinavir, diltiazem, verapamil and aprepitant
  - with significant electrolyte disturbances (e.g. hypokalaemia, hypomagnesaemia)
  - with underlying cardiac diseases such as congestive heart failure.

The dose of domperidone may be adjusted upward with caution to achieve the desired effect as needed. The expected benefit of an increased dose should outweigh the potential risks. The maximum dose of domperidone is 80 mg.

Domperidone should not be used in children.

The Product Information for domperidone has been updated to include the new drug dosage and usage recommendations, as well as information about the risk of serious ventricular arrhythmias and sudden cardiac death.

(See WHO Pharmaceuticals Newsletter No.2, 2012 and No. 2, 2007 for association with serious ventricular arrhythmias and sudden cardiac death in Canada).

Reference:
Medicines Safety Update Vol 3, No. 6, December 2012 (www.tga.gov.au).

Fingolimod

Cardiovascular safety risk

Australia. The TGA advised health-care professionals of important cardiovascular safety related changes to the fingolimod (Gilenya®) Product Information. Fingolimod is now contraindicated in patients with specific cardiac conditions and in patients with concomitant treatment with Class Ia or Class III anti-arrhythmic drugs during fingolimod initiation. The Precautions section has been updated to include first-dose monitoring, with emphasis on cardiac monitoring, namely pulse, blood pressure and electrocardiogram. Should a patient require pharmacological intervention during the first-dose observation, overnight monitoring in a medical facility should be instituted and the first-dose monitoring strategy should be repeated after the second dose of fingolimod.

(See WHO Pharmaceuticals Newsletter No. 1, 2012 for safety review of a reported death after the first dose in the USA and for review of fingolimod and advise to intensify cardiovascular monitoring after first dose in EU, No. 2, 2012 in Canada and No.3 2012 for New advice to better manage risk of adverse effects on the heart in Europe and the US).

Reference:
Medicines Safety Update Vol 3, No. 6, December 2012 (www.tga.gov.au).

Ondansetron

Product removal due to potential for serious cardiac risks

USA. The US FDA notified health-care professionals that the 32 mg, single intravenous (IV) dose of ondansetron hydrochloride (Zofran®) will no longer be marketed because of the potential for serious cardiac risks.

The 32 mg, single IV dose of ondansetron hydrochloride had been used to prevent chemotherapy-induced nausea and vomiting. A previous Drug Safety Communication (DSC), issued on June 29, 2012, communicated that the 32 mg, single IV dose should be avoided due to the risk of a specific type of irregular heart rhythm called QT interval prolongation, which can lead to Torsades de Pointes, an abnormal, potentially fatal heart rhythm. These drugs are sold pre-mixed in solutions of either dextrose or sodium chloride in plastic containers.

The US FDA continues to recommend the intravenous regimen of 0.15 mg/kg administered every 4 hours for three doses to prevent chemotherapy-induced nausea and vomiting. Oral dosing of Ondansetron remains effective for the prevention of chemotherapy-induced nausea and vomiting.

(See WHO Pharmaceuticals Newsletters No. 5, 2011 for risk of abnormal heart rhythms in the USA and Nos. 4 and 6

2012 for dose restriction in intravenous use due to dose-dependent QT interval prolongation).

Reference:
FDA Drug Safety Communication, US FDA 4 December 2012 (*www.fda.gov*).

Over-the-counter cough and cold medicines for children

Use in children

Australia. The TGA has recently completed a review of the safety and efficacy of over-the-counter cough and cold medicines for use in children.

The Agency concluded that these medicines:

- should not be given to children under 6 years of age
- should only be given to children aged 6 to 11 years on the advice of a doctor, pharmacist or nurse practitioner
- should be labelled with warnings and instructions to the above effect
- should only be available in child-resistant packaging.

The TGA advised health-care professionals that no changes have been made to the scheduling of these medicines and a prescription is not required. A recommendation for treatment with these medicines for a child less than 6 years of age constitutes off-label use.

Existing stock with older labelling can still be sold for adults and children aged 12 years and over (or 6 to 11 years on the advice of a health professional) until stocks are exhausted.

Reference:
Medicines Safety Update Vol 3, No. 6, December 2012 (www.tga.gov.au).

Sodium oxybate

Warning against use with alcohol or drugs causing respiratory depression

USA. The US FDA reminded health-care professionals and patients that the combined use of sodium oxybate (Xyrem®) with alcohol or central nervous system (CNS) depressant drugs can markedly impair consciousness and may lead to severe breathing problems (respiratory depression). The use of alcohol with the drug is a new contraindication added to the sodium oxybate label, which already contraindicates its use with insomnia drugs. The use with other CNS depressant drugs (drugs that affect the CNS and may lead to breathing problems) such as opioid analgesics, benzodiazepines, sedating antidepressants or antipsychotics, general anesthetics, and muscle relaxants should generally be avoided. The use of sodium oxybate along with these products or other CNS depressants increases the risk of breathing problems that may lead to loss of consciousness, coma, and death.

Sodium oxybate is approved to reduce attacks of muscle weakness (cataplexy) and treat daytime sleepiness in patients with narcolepsy by the US FDA. Sodium oxybate is also known as gamma-hydroxybutyrate (GHB). GHB is a known drug of abuse that has been associated with central nervous system (CNS) adverse events, including death. Even at recommended doses, the drug can cause confusion, depression, and other neuropsychiatric events.

The US FDA urged health-care professionals to follow the dosing recommendations, contraindications, and boxed warning in the updated drug label and to avoid drug combinations that raise the risk of respiratory depression and death. Patients should not drink alcohol or take insomnia drugs.

Reference:
FDA Drug Safety Communication, US FDA 17 December 2012 (*www.fda.gov*).

Statins

Risk of increased blood sugar levels and diabetes

Canada. Health Canada informed of a labelling update for statins regarding the risk of increased blood sugar levels and a small increased risk of diabetes among patients already at risk for the disease. Based on the review of all available data, Health Canada concluded that the risk of diabetes appears to be mainly in patients with pre-existing risk factors for diabetes, such as high levels of glucose or triglycerides, obesity or high blood pressure. Health Canada continues to believe the overall cardiovascular benefits of statin drugs in reducing blood cholesterol outweigh their risks.

A new warning about the increased blood sugar levels and the risk of diabetes, including information on how to identify high-risk patients, has been added to the drug labels for the six statins currently marketed in Canada: atorvastatin (Lipitor® and generics), lovastatin (Mevacor® and generics), rosuvastatin (Crestor® and generics), simvastatin (Zocor® and generics), pravastatin (Pravachol® and generics), fluvastatin (Lescol® and generics).

The new labels recommend that health-care professionals carefully monitor the use of statins in patients at a high risk of future diabetes.

Health Canada recommended patients who are on statins and experience symptoms associated with increased blood sugar, such as severe frequent urination, thirst or hunger, to contact their health-care professional.

Reference:
Advisories, Warnings and Recalls, Health Canada, 24 January 2013 (*www.hc-sc.gc.ca*).

Telaprevir

New boxed warning - serious skin reactions

USA. The US FDA announced that it received reports of serious skin reactions, some fatal, in patients taking the hepatitis C drug telaprevir (Incivek®) in combination with peginterferon alfa and ribavirin (Incivek combination treatment). Some patients died when they continued to receive Incivek combination treatment after developing a worsening, or progressive rash and systemic symptoms (symptoms affecting the entire body). The US FDA added a boxed warning to telaprevir drug label stating that Incivek combination treatment must be immediately stopped in patients experiencing the above.

Telaprevir is a hepatic C virus NS3/4A protease inhibitor indicated in combination with peginterferon alfa and ribavirin for the treatment of genotype 1 chronic hepatitis C in adult patients with compensated liver disease, including patients who have cirrhosis, are treatment-naïve, or who have been previously received interferon-based treatment.

Health-care professionals are recommended to make sure patients know that rash may occur with Incivek combination treatment, and explain the signs and symptoms of severe skin reaction and when to seek care. If serious skin reactions occur, all three components of Incivek combination treatment, including peginterferon alfa and ribavirin, must be immediately discontinued, and the patient should receive urgent medical care. Consideration should also be given to stopping any other medications that may be associated with serious skin reactions.

Reference:
FDA Drug Safety Communication, US FDA 19 December 2012 (*www.fda.gov*).

Tolvaptan

Potential risk of liver injury

USA. The US FDA and Otsuka, the manufacturer of tolvaptan (Samsca®), notified health-care professionals of significant liver injury associated with the drug. In a double-blind, 3-year, placebo-controlled trial in about 1400 patients with Autosomal Dominant Polycystic Kidney Disease (ADPKD) and its open-label extension trial, 3 patients treated with the drug developed significant increases in serum alanine aminotransferase (ALT) with concomitant, clinically significant increases in serum total bilirubin. In the trials the maximum daily dose of tolvaptan administered (90 mg in the morning and 30 mg in the afternoon) was higher than the maximum 60 mg daily dose approved for the treatment of hyponatremia.

Most of the liver enzyme abnormalities were observed during the first 18 months of therapy. Following discontinuation of treatment, all 3 patients improved. These data are not adequate to exclude the possibility that patients receiving tolvaptan for its indicated use of clinically significant hypervolemic and euvolemic hyponatremia are at increased risk for irreversible and potentially fatal liver injury.

The US FDA recommended that health-care providers should perform liver tests promptly in patients who report symptoms that may indicate liver injury, including fatigue, anorexia, right upper abdominal discomfort, dark urine or jaundice. If hepatic injury is suspected, tolvaptan should be promptly discontinued, appropriate treatment should be instituted, and investigations should be performed to determine probable cause. tolvaptan should not be re-initiated in patients unless the cause for the observed liver injury is definitively established to be unrelated to treatment with tolvaptan.

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

Zolpidem containing products

Lower recommended doses required

USA. The US FDA recommended that the bedtime dose of zolpidem be lowered because new data show that blood levels in some patients may be high enough the morning after use to impair activities that require alertness, including driving. This announcement focuses on zolpidem products approved for bedtime use, which are marketed as generics and under the brand names Ambien®, Ambien CR®, Edluar®, and Zolpimist™.

Data showed that the risk for next-morning impairment is highest for patients taking the extended-release forms of these drugs (Ambien CR® and generics). Women appear to be more susceptible to this risk because they eliminate zolpidem from their bodies

more slowly than men. Because use of lower doses of zolpidem will result in lower blood levels in the morning, the US FDA required the manufacturers of these drugs to lower the recommended dose. The recommended doses of Intermezzo®, a lower dose zolpidem product approved for middle-of-the-night awakenings, are not changing. At the time of Intermezzo's approval in November 2011, the label already recommended a lower dosage for women than for men.

The US FDA reminded the public that all drugs taken for insomnia can impair driving and activities that require alertness the morning after use.

The US FDA recommended that;

- The dose of zolpidem for women should be lowered from 10 mg to 5 mg for immediate-release products (Ambien®, Edluar®, and Zolpimist™) and from 12.5 mg to 6.25 mg for extended-release products (Ambien CR®).
- For zolpidem and other insomnia drugs, the lowest dose that treats the patient's symptoms should be prescribed.
- Patients should be informed that impairment from sleep drugs can be present despite feeling