WHO PHARMACEUTICALS NEWSLETTER

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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Contents

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The WHO Pharmaceutical Newsletter provides you with the latest information on the safety of medicines and legal actions taken by regulatory authorities across the world.

In this issue of the Newsletter we also bring you a feature on a WHO training course on pharmacovigilance that was held in New Delhi. The training course was a part of the WHO strategy to help establish at least the minimum standards for pharmacovigilance. A special feature was the module on safety surveillance in preventive chemotherapy for the control of neglected tropical diseases.

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TABLE OF CONTENTS

Regulatory Matters

Safety of Medicines

Feature

Antipsychotics

Class labelling change to advise on use during pregnancy and risk of abnormal muscle movements and withdrawal symptoms in newborns

USA. The U.S. Food and Drug Administration (US FDA) notified health-care professionals that the Pregnancy section of drug labels for the entire class of antipsychotic medicines has been updated to include consistent information about the potential risk for extrapyramidal signs (EPS) and withdrawal symptoms in newborns whose mothers were treated with these medicines during the third trimester of pregnancy. The EPS and withdrawal symptoms in newborns may include agitation, abnormally increased or decreased muscle tone, tremor, sleepiness, severe difficulty of breathing, and difficulty in feeding. In some newborns, the symptoms subside within hours or days and do not require specific treatment; other newborns may require longer hospital stays.

The US FDA advises that health-care professionals should be aware that neonates exposed to antipsychotic medications during the third trimester of pregnancy are at risk for EPS and/or withdrawal symptoms following delivery.

Reference:
FDA Drug Safety Communication, US FDA, 22 February 2011 (www.fda.gov)

Buflomedil

Marketing authorizations suspended

France. The French Health Products Safety Agency (Afssaps) decided on the suspension of the marketing authorizations of buflomedil containing products on 11 February 2011. All batches of buflomedil-containing products were recalled in France on 17 February 2011. The action was taken following notification of serious nervous (convulsions, myoclonia and status epilepticus) and cardiac (tachycardia, hypotension, ventricular rhythm disorders and cardiac arrest) events especially in accidental overdose or voluntary overdose.

(See WHO Pharmaceuticals Newsletter No.1, 2007 for the decision by Afssaps to withdraw buflomedil 300 mg tablets from the market due to the risk of suicide.)

Reports in WHO Global ICSR database, Vigibase:

Buflomedil

Number of reports: 387 (SOC Cardiovascular Disorders, General, SOC Central & Peripheral Nervous System Disorders, SOC Heart Rate and Rhythm Disorders)

Most reported reactions (number of events):

Hypotension:	*35*
Dizziness:	*41*
Headache:	*35*
Tremor:	*39*
Vertigo:	*36*
Convulsions:	*56*
Tachycardia:	*31*

Reference:
Spécialités à base de Buflomédil - Retrait de produits, Afssaps, 17 February 2011 (www.afssaps.fr)

Dipeptidyl peptidase-4 inhibitors and glucagon-like peptide-1 receptor agonists

Possible glycaemic complications

Japan. The Ministry of Health, Labour and Welfare, Japan (MHLW) warned about the risk of hypoglycaemia associated with concomitant use of dipeptidyl peptidase-4 (DPP-4) inhibitors and sulfonylureas, and the risk of diabetic ketoacidosis and hyperglycaemia after switching from insulin to glucagon-like peptide-1 (GLP-1) receptor agonists. DPP-4 inhibitors and GLP-1 receptor agonists are anti-diabetic drugs with new action mechanisms.

DPP-4 inhibitors inhibit DPP-4, which inactivates incretin. Incretin is a gastrointestinal hormone which stimulates the insulin secretion depending on the blood glucose level. DPP-4 inhibitors are used to treat type 2 diabetes mellitus by increasing the endogenous active incretin level and thereby controlling the blood glucose. As of December 2010, sitagliptin phosphate hydrate, vildagliptin, and alogliptin benzoate of this class have been approved in Japan.

GLP-1 receptor agonists are used to treat type 2 diabetes mellitus by binding to the GLP-1 receptor to promote insulin secretion in response to the increase in blood glucose. As of December 2010, liraglutide (genetical recombination) and exenatide have been approved.

The MHLW says that 28 cases of hypoglycaemia following administration of a DPP-4 inhibitor sitagliptin phosphate hydrate were reported from 11 December 2009 (the date of the initial marketing)

through 19 April 2010. Among them, causality could not be denied in 25 cases, including eight cases in which loss of consciousness occurred after hypoglycaemia. In 21 of the 25 cases, sulfonylureas (SUs) were concomitantly used. In eight cases, patients received the maximum dose of SU, which exceeded the maintenance dose. Therefore, the MHLW required marketing authorization holders (MAHs) in April 2010 to revise the package insert of sitagliptin phosphate hydrate to include the following.

- The increased risk of hypoglycaemia especially with concomitant use of SU.
- Serious hypoglycaemia followed by loss of consciousness reported in patients treated with concomitant use of SU.
- Dose reduction of SU to be considered when used concomitantly with sitagliptin to lower the risk of SU-induced hypoglycaemia.

The package inserts of the other DPP-4 inhibitors (vildagliptin and alogliptin benzoate) were also revised to include the same warnings about possible hypoglycaemia. In addition, the same alerts were added in the package insert of liraglutide (GLP-1 receptor agonist), since liraglutide is an incretin analogue that binds to the GLP-1 receptor to promote insulin secretion.

The MHLW also states that two fatal cases of diabetic ketoacidosis associated with liraglutide have been reported from 11 June 2010 (the date of the initial marketing) though 24 September 2010. Since insulin had been switched to liraglutide in both cases, the information to ensure proper use of the medicine was provided to medical institutions, specifically, not to switch insulin to liraglutide in patients with type 1 diabetes or type 2 diabetes requiring insulin therapy. Liraglutide is contraindicated for patients with type 1 diabetes lacking insulin secretion, and should be carefully administered to patients with type 2 diabetes requiring insulin therapy. Up to 7 October 2010, four cases of diabetic ketoacidosis (two fatal cases) and 16 cases of hyperglycaemia had been reported. In 17 of the 20 cases, the events occurred after insulin was switched to liraglutide. Therefore, the MHLW required MAHs on 12 October 2010 to revise the package insert of liraglutide to include the following.

- Liraglutide is not an alternative to insulin.
- Use of liraglutide should be determined based on the patient's insulin dependence.
- Sudden hyperglycaemia and diabetic ketoacidosis has occurred in insulin-dependent patients after switching from insulin to liraglutide.

Reference:
Pharmaceuticals and Medical Devices Safety Information No.275, MHLW, December 2010, (*www.pmda.go.jp/english*).

Dronedarone

Risk of hepatocellular liver injury

Canada. Health Canada and Sanofi-Aventis Canada Inc. advised about the risk of hepatocellular liver injury in association with dronedarone (Multaq®). Dronedarone is indicated for the treatment of patients with a history of, or current atrial fibrillation to reduce the risk of hospitalization due to atrial fibrillation. According to the company, there have been 155 post-marketing cases (87 serious cases) reporting hepatobiliary adverse events, including rare cases of hepatic failure. Some cases were suspected of drug-induced hepatic injury with a predominant hepatocellular pattern of injury, including two post-marketing case reports outside Canada of acute hepatic failure requiring transplantation. A definitive causal relationship between dronedarone and these cases has not been established.

Health-care professionals are advised that if hepatic injury is suspected, dronedarone should be discontinued immediately and followed by necessary blood tests. Patients treated with dronedarone should be advised to immediately report symptoms suggesting hepatic injury (such as anorexia, nausea, vomiting, fatigue, right upper abdominal quadrant pain, jaundice, dark urine or itching). The use of dronedarone in patients who have sustained liver injury is not recommended. The Canadian Product Monograph was revised to include this new safety information.

(See WHO Pharmaceuticals Newsletter No.1, 2011 for warnings about the risk of severe liver injury in Europe and the USA as well as reports in WHO Global ICSR database.)

Reference:
Advisories, Warnings and Recalls, Health Canada, 16 March 2011 (*www.hc-sc.gc.ca*).

Lopinavir/ritonavir

Label change due to serious health problems in premature babies

USA. The US FDA notified health-care professionals of serious health problems that have been reported in premature babies receiving lopinavir/ritonavir (Kaletra) oral solution. Kaletra oral solution is an antiviral medicine that is used in combination with other antiretroviral medicines for the treatment of HIV-1 infection in paediatric patients 14 days of age (whether premature or full term) or older and in adults. Kaletra oral solution contains alcohol and propylene glycol as excipients. When administered concomitantly with propylene glycol, ethanol competitively inhibits the metabolism of propylene glycol, which may lead to elevated concentrations of propylene glycol. Preterm neonates may be at increased risk of propylene glycol-associated adverse events due to diminished ability to metabolize propylene glycol, thereby leading to accumulation and potential adverse events such as serious heart, kidney or breathing problems. The US FDA states that because the consequences of using Kaletra oral solution in babies immediately after birth can be severe or possibly fatal, the label is being revised to include a new warning.

Health-care professionals are advised of the following.

- The use of Kaletra oral solution should be avoided in neonates before a postmenstrual age of 42 weeks and a postnatal age of at least 14 days has been attained.
- Kaletra oral solution should be avoided in preterm neonates in the immediate postnatal period because of possible toxicities. A safe and effective dose of Kaletra oral solution in these populations is not established.
- If in the judgment of the health-care professional, the benefit of using Kaletra oral solution in babies to treat HIV infection immediately after birth outweighs the potential risks, then the neonate should be monitored closely for increases in serum osmolality and serum creatinine and for toxicity related to Kaletra oral solution. These toxicities include hyperosmolality with or without lactic acidosis, renal toxicity, CNS depression (including stupor, coma, and apnoea), seizures, hypotonia, cardiac arrhythmias, ECG changes and haemolysis.
- Calculate the appropriate dose of Kaletra oral solution for each child based on body weight (kg) or body surface area (BSA) to avoid underdosing or exceeding the recommended adult dose.
- The total amounts of alcohol and propylene glycol from all medications that are to be given to paediatric patients from 14 days to six months of age should be taken into account in order to avoid toxicity from these excipients.
- Be aware that toxicity in preterm neonates can be severe or possibly fatal, and it can be mistaken for neonatal sepsis. Immediate discontinuation of the drug is critical in these settings.

(See WHO Pharmaceuticals Newsletter No.5, 2007 for caution against accidental overdose in children in the Netherlands and the UK.)

***Reference**:*

FDA Drug Safety Communication, US FDA, 8 March 2011 (www.fda.gov).

Methylene blue injectable

Risk of serotonin toxicity

Canada. Health Canada issued a warning that cases of serotonin toxicity have been reported and published in association with the use of methylene blue (methylthioninium chloride) injectable in patients exposed to drugs with serotonin reuptake inhibition properties, e.g. selective serotonin reuptake inhibitors (SSRIs). The cases of serotonin toxicity (also known as serotonin syndrome) involved agitation, diaphoresis or hypertonia accompanied with pyrexia (> 38° C), and tremor, hyperreflexia or clonus (spontaneous, inducible or ocular). Health Canada states that the prescribing information of methylene blue injectable products will be updated to include the following points.

- Serotonin toxicity/serotonin syndrome has been reported when methylene blue was administered intravenously in patients also receiving other drugs having serotonin reuptake inhibition properties. Several of these cases required admission to intensive care unit.
- If drugs with serotonin reuptake inhibition properties are being taken, careful consideration needs to be given to stop them before methylene blue injectable use and allow a washout period equivalent to at least four to five half-lives.

Health Canada explains that recent research has revealed that methylene blue has structural properties similar to monoamine oxidase inhibitors (MAOI), which are known precipitants of serotonin toxicity when administered concomitantly with drugs having serotonin reuptake inhibition properties. Serotonin toxicity has been reported when methylene blue was administered intravenously at concentrations as low as 1 mg/kg, in patients receiving SSRIs or other drugs with SSRI properties (e.g., duloxetine, venlafaxine and clomipramine). Several of these cases required admission to the intensive care unit.

(See WHO Pharmaceuticals Newsletter No.3, 2009 for a warning in the UK about the risk of central nervous system toxicity associated with an interaction between methylthioninium chloride (methylene blue) and a serotoninergic drug.)

Reference:
Advisories, Warnings and Recalls, Health Canada, 17 February 2011 (www.hc-sc.gc.ca).

Modafinil

Restricted to narcolepsy

UK. The MHRA advised about the use of modafinil, following European-wide restriction of use of modafinil to the narcolepsy indication. Modafinil (Provigil®) is indicated for the treatment of excessive sleepiness in adults with narcolepsy, with or without cataplexy. Modafinil is no longer indicated for shift-worker sleep disorder and obstructive sleep apnoea. The Agency's advice for health-care professionals is as follows.

- Modafinil should not be used in the following groups: those with uncontrolled hypertension or cardiac arrhythmias; children up to 18 years old; women who are pregnant or breastfeeding.
- Modafinil should be discontinued and not restarted in cases of: serious skin or hypersensitivity reactions; psychiatric disorders such as suicidal ideation.
- A baseline electrocardiogram should be done before treatment initiation. Patients with abnormal findings should be further evaluated by specialists before modafinil treatment can be initiated.
- Cardiovascular function, especially blood pressure and heart rate, should be monitored regularly. Such patients should be monitored closely and advised to report any suspected adverse behaviours or thoughts. Patients should be assessed immediately and treatment stopped if appropriate.

(See WHO Pharmaceuticals Newsletter No.5, 2010 for a review of the benefits and risks of modanifil in Europe.)

References:
Drug Safety Update, March 2011, Volume 4, Issue 8, A1, MHRA (www.mhra.gov.uk).

Proton pump inhibitors

Labelling change

USA. (1) The US FDA notified health-care professionals and the public that prescription proton pump inhibitor (PPI) drugs (including esomeprazole, dexlansoprazole, omeprazole, lansoprazole, pantoprazole and rabeprazole) may cause hypomagnesaemia if taken for prolonged periods of time (in most cases, longer than one year). The Agency warns that low serum magnesium levels can result in serious adverse events including tetany, arrhythmias and seizures. Treatment of hypomagnesaemia generally

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