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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This Newsletter is also available on our Internet website:
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No. 2, 2011

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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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. Modafinil should be discontinued in patients who develop arrhythmia or moderate to severe hypertension, and should not be restarted until the condition has been adequately evaluated and treated.
- Modafinil should be used with caution in patients with a history of: psychosis, depression, or mania; abuse of alcohol, drugs or illicit substances. 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 requires magnesium supplements. The Agency says that in approximately one-quarter of the cases reviewed, magnesium supplementation alone did not improve low serum magnesium levels and the PPI had to be discontinued. PPIs are used to treat conditions such as gastroesophageal reflux disease, stomach and small intestine ulcers and inflammation of the oesophagus.

The recommendations from the US FDA for health-care professionals include the following.

- Consider obtaining serum magnesium levels prior to initiation of prescription PPI treatment and checking levels periodically thereafter for patients expected to be on prolonged treatment or who take PPIs with medications such as digoxin or drugs that may cause hypomagnesaemia (e.g. diuretics).
- Hypomagnesaemia occurs with both loop diuretics (furosemide, bumetanide, torsemide and ethacrynic acid) and thiazide diuretics (chlorothiazide, hydrochlorothiazide, indapamide and metolazone). These agents can cause hypomagnesaemia when used as a single agent or when combined with other anti-hypertensives (e.g. beta-blockers, angiotensin receptor blockers and/or ACE inhibitors).
- Advise patients to seek immediate care from a health-care professional if they experience arrhythmias, tetany, tremors or seizures while taking PPIs. These may be signs of hypomagnesaemia.
- Consider PPIs as a possible cause of hypomagnesaemia, particularly in patients who are clinically symptomatic.
- Patients who develop hypomagnesaemia may require PPI discontinuation in addition to magnesium replacement.

Information about the potential risk of low serum magnesium levels from PPIs will be added to the labels for all the prescription PPIs. With regard to OTC PPIs, the US FDA states that OTC PPIs are marketed at low doses and are only intended for a 14 day course of treatment up to three times per year, and that there is very little risk of hypomagnesaemia when OTC PPIs are used according to the directions on the OTC label.

(2) The US FDA has determined that an osteoporosis and fracture warning on the over-the-counter (OTC) proton pump inhibitor (PPI) medication 'Drug Facts' label is not indicated at this time. Following a review of available safety data, the Agency has concluded that fracture risk with short-term, low dose PPI use is unlikely. This is an update on the May 2010 announcement that the prescription and OTC labels for PPIs were revised to include information about a possible increased risk of fractures of the hip, wrist and spine with the use of PPIs. (See WHO Pharmaceuticals Newsletter No.4, 2010) The US FDA says that the available data show that patients at highest risk for fractures received high doses of prescription PPIs (higher than OTC PPI doses) and/or used a PPI for one year or more. In contrast to prescription PPIs, OTC PPIs are marketed at low doses and are only intended for a 14 day course of treatment up to three times per year.

Reference:
(1) FDA Drug Safety Communication, US FDA, 2 March 2011 (www.fda.gov).
(2) FDA Drug Safety Communication, US FDA, 22 March 2011 (www.fda.gov).

Rosiglitazone

Suspension of rosiglitazone (Avandia and Avandamet)

New Zealand. Medsafe (New Zealand Medicines and Medical Devices Safety Authority) announced that the consent to distribute rosiglitazone-containing medicines will be suspended in New Zealand from 29 April 2011. The suspension will remain in place until the company that developed rosiglitazone identifies a population of patients for whom the benefits of treatment outweigh the risks. This follows the review by the Medicines Adverse Reactions Committee (MARC) of the benefits and risks of treatment with rosiglitazone. The MARC considered that data from meta-analyses and observational studies demonstrated an increased risk of myocardial infarction. Medsafe has advised patients not to stop taking rosiglitazone, but they should contact their doctor to discuss alternative treatments.

(See WHO Pharmaceuticals Newsletters No.6, 2010 for new restrictions due to the risk of cardiovascular events in Canada and No.5, 2010 for suspension of marketing authorizations in Europe, new restrictions in the USA and reports in WHO global ICSR database.)

Reference:
Prescriber Update Vol. 32, No.1 March 2011, (www.medsafe.govt.nz).

Rotavirus vaccination

Risk of intussusception

Australia. The Therapeutic Goods Administration (TGA) has published a report of its investigation of a possible association between the use of the rotavirus vaccines Rotarix® (GSK) and RotaTeq® (Merck/CSL) and the occurrence of a rare form of bowel obstruction known as intussusception (IS).

In Australia, two post-marketing studies have been conducted to investigate whether the two rotavirus vaccines are associated with an increased risk of IS. The first study was conducted using two surveillance systems, the Paediatric Enhanced Disease Surveillance (PAEDS) with active surveillance of IS cases in four tertiary centres, and the Australian Paediatric Surveillance Unit (APSU) with national retrospective reporting of IS cases by paediatricians.

This study found an apparent four-fold increased risk of IS in babies within one week of being given the first dose of either vaccine, compared with historical data on hospitalisations coded as IS, but no overall increase in overall rates of IS up to the age of nine months. Following the first study, a large self-controlled case series study using data on all hospitalised cases coded as IS was conducted. This study found a statistically significant four-fold increase in the occurrence of IS in the first one to seven days following the first dose of either Rotarix or RotaTeq compared with other time periods after vaccine receipt. This increase in risk translates to approximately two additional cases of IS occurring in every 100 000 first doses of vaccine administered, or six additional cases each year in children under 12 months of age in Australia. (These findings are preliminary.) The TGA comments that it is currently unclear whether this represents a true increase in overall risk of IS, or an early increase in risk of IS in infants which is compensated for by a subsequent decrease in risk leading to a reduction in cases of IS in older children.

The TGA concludes that its analysis provides evidence that both registered rotavirus vaccines are likely to be associated with an increase in risk of IS in the seven days following the first dose of both Rotarix and RotaTeq. However, the TGA considers that the overall risk benefit balance of both vaccines remains positive. The TGA states that prior to the introduction of rotavirus vaccine, an estimated 10 000 hospital admissions occurred annually in children under five years due to rotavirus gastroenteritis. Since the introduction of Rotarix and RotaTeq on to the National Immunisation Program, emergency department visits for acute gastroenteritis in young children have declined and hospitalisations for rotavirus gastroenteritis in the under five year age group have been reduced by over 70%. The Product Information documents for the two vaccines will be amended to reflect the findings.

Reference:
Safety information, Alerts/advisories, TGA, 25 February 2011 (www.tga.gov.au).

Sitaxentan

Withdrawal of the marketing authorisation in the European Union

Europe. The European Medicines Agency (EMA) announced the withdrawal of the marketing authorization of sitaxentan (Thelin)®. Sitaxentan is an endothelin receptor antagonist used to treat adults (aged 18 years or over) with pulmonary arterial hypertension. Sitaxentan had been known to be associated with liver toxicity and had been contra-indicated in patients with mild to severe hepatic impairment and elevated aminotransferases prior to initiation of treatment. In December 2010, the marketing authorisation holder requested the withdrawal of the marketing authorisation in the interest of patient safety in response to new information on two cases of fatal liver injury. On 6 January 2011, the European Commission issued a decision confirming the withdrawal of the marketing authorization of Thelin.

(See WHO Pharmaceuticals Newsletter No.1, 2011 for worldwide withdrawal due to cases of unpredictable serious liver injury.)

Reference:
Press releases, EMA, 22 March 2011 (www.ema.europa.eu).

Terbutaline

New warnings against use of terbutaline to treat preterm labour

USA. The U.S. Food and Drug Administration (US FDA) has notified the public that injectable terbutaline should not be used in pregnant women for prevention or prolonged treatment (beyond 48 to 72 hours) of preterm labour in either the hospital or outpatient setting because of the potential for serious maternal heart problems and death. The labelling of terbutaline injection will be revised to add a Boxed Warning and Contraindication to warn against this use. In addition, oral terbutaline should not be used for prevention or any treatment of preterm labour because it has not been shown to be effective and has similar safety concerns. The labelling of terbutaline tablet will be revised to add a Boxed Warning and Contraindication to warn against this use. These actions follow after the US FDA has reviewed post-marketing safety reports of terbutaline used for obstetrical indications, as well as data from the medical literature.

The Agency warns that death and serious adverse reactions, including increased heart rate, transient hyperglycaemia, hypokalaemia, cardiac arrhythmias, pulmonary oedema and myocardial ischaemia have been reported after prolonged administration of oral or injectable terbutaline to pregnant women. Terbutaline is approved to prevent and treat bronchospasm associated with asthma, bronchitis and emphysema. The US FDA says that terbutaline is sometimes used off-label for acute obstetric uses, including treating preterm labour and treating uterine hyperstimulation, and that the medicine has also been used off-label over longer periods of time in an attempt to prevent recurrent preterm labour.

The US FDA has concluded that the risk of serious adverse events outweighs any potential benefit to pregnant women receiving prolonged treatment with terbutaline injection (beyond 48 to 72 hours), or acute or prolonged treatment with oral terbutaline. The Agency advises health-care professionals that there are certain obstetrical conditions where the health-care professional may decide that the benefit of terbutaline injection for an individual patient in a hospital setting clearly outweighs the risk. However, the prolonged use of this medicine to prevent recurrent preterm labour can result in maternal heart problems and death. Terbutaline should not be used in the outpatient or home setting.

Reports in WHO Global ICSR database, Vigibase:

Terbutaline (Intravenous, parenteral)

Number of reports: 54 (SOC Body as a Whole - General Disorders, SOC Cardiovascular Disorders, General, SOC Heart Rate and Rhythm Disorders, SOC Reproductive Disorders, Female)

Most reported reactions (number of events):

Condition aggravated:	*10*
Chest pain:	*5*
Death:	*5*
Medicine ineffective:	*11*
Hypotension:	*6*
Tachycardia:	*14*

References:

FDA Drug Safety Communication, US FDA, 17 February 2011 (www.fda.gov).

Topiramate

Label change due to the risk for development of cleft lip and cleft palate in newborns

USA. The US FDA notified health-care professionals and patients of an increased risk of development of cleft lip and/or cleft palate in infants born to women treated with topiramate during pregnancy. Topiramate is an anticonvulsant medication that is approved for use alone or with other medications to treat patients with epilepsy who have certain types of seizures. Topiramate is also approved for use to prevent migraine headaches. The US FDA explains that data from the North American Antiepileptic Drug (NAAED) Pregnancy Registry, a group that collects information about outcomes in infants born to women treated with antiepileptic drugs during pregnancy, indicate an increased risk of oral clefts in infants exposed to topiramate monotherapy during the first trimester of pregnancy. Because of the increased risk for oral clefts, topiramate is being placed in Pregnancy Category D, which means that there is positive evidence of foetal risk based on human data, but the benefits of the medicine in pregnant women may outweigh the risks in certain situations. The patient medication guide and prescribing information for topiramate will be updated with the new information.

The US FDA advises that the benefits and the risks of topiramate should be carefully weighed when prescribing this medicine to women of childbearing age, particularly for conditions not usually associated with permanent injury or death. Alternative medications that have a lower risk of oral clefts and other adverse birth outcomes should be considered for these patients. If the decision is

made to prescribe topiramate to women of childbearing age, health-care professionals should recommend use of effective contraception for women who are not planning a pregnancy, keeping in mind the potential for a decrease in hormonal exposure and a possible decrease in contraceptive efficacy when using oestrogen-containing birth control with topiramate. Oral clefts occur in the first trimester of pregnancy before many women know they are pregnant.

Reports in WHO Global ICSR database, Vigibase:

Topiramate

Number of reports: 41 (SOC Foetal Disorders)

Reported reactions (number of events):

Cleft palate (including cleft lip): 47

Reference:
FDA Drug Safety Communication, US FDA, 4 March 2011 (www.fda.gov)

Abacavir

Safety review update of abacavir and possible increased risk of heart attack

USA. The US FDA has issued an update on its ongoing safety review of abacavir and a possible increased risk of heart attack. Abacavir is an antiviral medication that is used in combination with other antiretroviral drugs for the treatment of HIV-1 infection. There has been conflicting information on the potential increased risk of myocardial infarction with abacavir treatment. The US FDA conducted a meta-analysis of 26 randomized clinical trials that evaluated abacavir. The Agency states that this meta-analysis did not show an increased risk of myocardial infarction associated with the use of abacavir. Health-care professionals are advised to continue to prescribe abacavir according to the professional label. Patients are advised not to stop taking their abacavir without first talking to their health-care professional. The US FDA says that it will continue to communicate any new safety information to the public as it becomes available.

Reference:
FDA Drug Safety Communication, US FDA, 1 March 2011 (www.fda.gov)

Colchicine

Warning about toxicity and interactions

New Zealand. Medsafe advised that the lowest effective dose of colchicine should be used and must not exceed six mg over four days. Elderly patients and patients with hepatic or renal impairment are at higher risk of colchicine toxicity. Colchicine should not be used in patients with hepatic or renal impairment who are also taking CYP3A4 and P-glycoprotein inhibitors.

Colchicine is approved for the treatment of acute gout when non-steroidal anti-inflammatory drugs are contraindicated or have previously been unsuccessful. Colchicine has a low threshold for toxicity. Medsafe explains in the *Prescriber Update* that colchicine is metabolised by cytochrome P450 3A4 (CYP3A4) and excreted via the P-glycoprotein (P-gp) transport system. For patients with renal or hepatic impairment, concurrent administration of colchicine with strong CYP3A4 inhibitors or P-gp inhibitors is contraindicated. For patients with normal renal and hepatic function, a reduction in colchicine dose is recommended when concurrent treatment with a strong CYP3A4 inhibitor or a P-gp inhibitor is required. Strong CYP3A4 inhibitors include protease inhibitors, imidazoles and clarithromycin; moderate inhibitors include simvastatin and erythromycin. Inhibitors of P-gp include cyclosporine, ketoconazole, protease inhibitors, and tacrolimus. Medsafe advises that symptoms of colchicine toxicity may be delayed by up to 12 hours; therefore all patients who are suspected of taking an overdose should be referred for immediate medical assessment. All patients should be monitored for 24 hours. Early symptoms include abdominal pain, nausea, vomiting and diarrhoea. Symptoms occurring after one to seven days include: confusion, cardiac, renal and hepatic impairment, respiratory distress, hyperpyrexia and bone marrow depression.

(See WHO Pharmaceuticals Newsletters No.1, 2010 for the risk of serious and fatal toxicity in overdose in the UK and No. 1, 2006 and 4, 2006 for related warnings in New Zealand.)

Reference:
Prescriber Update Vol. 32, No.1 March 2011, (www.medsafe.govt.nz).

Daptomycin

Risk of eosinophilic pneumonia

UK. The MHRA alerted health-care professionals that there have been rare but potentially serious reports of eosinophilic pneumonia associated with daptomycin (Cubicin). Daptomycin is indicated for the treatment of complicated skin and soft-tissue infections; right-sided infective endocarditis due to Staphylococcus aureus; and S aureus bacteraemia when associated with right-sided infective endocarditis or with complicated skin and soft-tissue infections. According to the Drug Safety Update, since daptomycin was licensed in 2006, there have been case reports globally of eosinophilic pneumonia and pulmonary eosinophilia associated with use of daptomycin. The MHRA states that although the exact incidence of eosinophilic pneumonia associated with daptomycin is unknown, to date the reporting rate is very low (<1/10 000). In severe cases, hypoxic respiratory insufficiency requiring mechanical ventilation may occur. The most common symptoms of eosinophilic pneumonia include cough, fever and dyspnoea. Most cases have occurred after two weeks of treatment.

The MHRA advises that if eosinophilic pneumonia is suspected, daptomycin should be discontinued immediately

and that if appropriate, the patient should be treated with corticosteroids. Daptomycin should not be re-administered to patients who have experienced eosinophilic pneumonia with this medicine.

(See WHO Pharmaceuticals Newsletters No.5, 2010 for a warning about the risk of eosinophilic pneumonia in the USA)

Reference:
Drug Safety Update, February 2011, Volume 4, Issue 7, A2, MHRA (www.mhra.gov.uk).

Dronedarone

Risk of cardiac failure and of hepatotoxicity

UK. The MHRA warned that the use of dronedarone (Multaq®) may be associated with an elevated risk of worsening or new-onset heart failure and liver toxicity. Dronedarone is an anti-arrhythmic agent that is indicated in adult, clinically stable patients with history of, or current, non-permanent atrial fibrillation (AF) to prevent recurrence of AF or to lower ventricular rate. Dronedarone is contraindicated in patients who are haemodynamically unstable, including those with symptoms of heart failure at rest or with minimal exertion.

According to the Drug Safety Update, up to 16 January 2011, 257 serious cases of new-onset or worsening heart failure (or suspected reactions synonymous with heart failure) have been reported worldwide. In addition, case reports of liver injury, including two cases of liver failure requiring transplantation, have been reported in patients receiving dronedarone. Some of these cases have occurred shortly after start of treatment.

For cardiac risk, health-care professionals are advised to consider suspending or discontinuing dronedarone if heart failure develops or worsens. For hepatic risk, health-care professionals are advised to perform liver-function tests regularly for patients prescribed dronedarone, and if alanine transaminase (ALT) levels are confirmed to be ≥3× upper limit of normal after retesting, dronedarone treatment should be withdrawn. Patients should be advised to consult a physician if they develop or experience worsening signs or symptoms of heart failure, such as weight gain, dependent oedema or increased dyspnoea, and/or if they develop any of the following symptoms of liver injury: abdominal pain or discomfort; loss of appetite; nausea; vomiting; yellowing of the skin or the whites of the eyes; unusual darkening of the urine; itching; or fatigue.

(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:
Drug Safety Update, February 2011, Volume 4, Issue 7, A1, MHRA (www.mhra.gov.uk).

H1N1 influenza vaccine (Pandemrix)

Further study results awaited on narcolepsy and possible association with Pandemrix

Europe. (1) The European Medicines Agency (EMA) announced that the Agency's Committee for Medicinal Products for Human Use (CHMP) has reviewed further data from Finland on the suspected link between narcolepsy in children and adolescents and Pandemrix. The Committee concluded that the new evidence added to the concern arising from case reports in Finland and Sweden, but that the data were still insufficient to establish a causal relationship between Pandemrix and narcolepsy. At present, no changes to the recommendations for use of Pandemrix are proposed. A variety of research efforts are now ongoing to understand the nature of any relationship between vaccination and narcolepsy, and the EMA states that it will provide updates as new information becomes available.

Sweden. (2) The Medical Products Agency (MPA) has issued a press release about the results from a Swedish registry-based cohort study indicate a 4-fold increased risk of narcolepsy in children and adolescents below the age of 20, vaccinated with Pandemrix, compared to children of the same age that were not vaccinated. The results are in line with those of a similar Finish registry study.

All cases of diagnosed narcolepsy reported to the healthcare databases in four regions of Sweden between October 1, 2009 and December 31, 2010 have been linked to information in the regional vaccination databases. These four regions have around 5.3 million inhabitants, which corresponds to roughly 57 percent of the Swedish population. The vaccination coverage was on average 67% for children and adolescents under the age of 20, and 51% for adults. The risk translates to an absolute risk of 3 cases of narcolepsy in 100 000 vaccinated children/adolescents. No increased risk was seen in adults.

The MPA concluded that vaccination of children and adolescents with Pandemrix for

the time being should not be recommended. The MPA will continue the investigation in order to seek explanations to the increased risk of narcolepsy in children and adolescents shown in the registry studies.

In an additional press release the same day MPA emphasises that adverse reaction reports and the result from the registry studies indicate that the risk of narcolepsy that can be related to Pandemrix is regarded as very small 12 months or more after vaccination.

France (3) The French agency Afssaps have in a press release announced that more cases of narcolepsy than expected have been reported in children of the age group 10 – 15 years, vaccinated with Pandemrix. According to the press release, a total of 25 cases of narcolepsy have been reported in France among 5.7 million vaccinated. Of these 4.1 million have been vaccinated with Pandemrix where 23 cases have been reported, while in the 1.6 million vaccinated with Panenza only two cases have been reported. No increase of narcolepsy was seen in other age groups.

References:

(1) Press release, EMA, 18 February 2011 (www.ema.europa.eu).
(2) Press release, MPA, 29 March 2011 (www.lakemedelsverket.se)
(3) Press release, Afssaps, 4 April 2011 (www.afssaps.fr)

Lenalidomide

Risk of thrombosis and thromboembolism

UK. The MHRA warned about the risk of thrombosis and thromboembolism in association with use of lenalidomide. Lenalidomide (Revlimid®) is authorised in combination with dexamethasone for treatment of multiple myeloma in patients who have received at least one previous treatment. Multiple myeloma is an independent risk factor for thromboembolic complications. The MHRA states that evidence from clinical trials and case reports of adverse drug reactions suggests that lenalidomide may further increase the elevated risk of both venous and arterial thromboembolic reactions, including myocardial infarction and cerebrovascular accident, in patients with myeloma.

According to the Drug Safety Update, 493 reports of arterial thromboembolic events had been received by the licence holder from all sources worldwide up to 26 December 2009. The licence holder had also received 1079 reports of venous thromboembolic events up to 26 December 2009, comprising mainly deep venous thrombosis, with or without pulmonary embolism. Through the UK Yellow Card Scheme, up to 7 December 2010, there have been two reports of myocardial infarction and two reports of stroke in association with use of lenalidomide. Venous thromboembolic events reported in the UK comprise pulmonary embolism (eight cases), deep venous thrombosis (four cases), and unspecified thrombosis (two cases).

The MHRA provides the following advice for health-care professionals.

- Patients receiving lenalidomide for the management of multiple myeloma should be closely monitored for evidence of arterial and venous thromboembolic events.
- Modifiable risk factors for thromboembolic events should be managed wherever possible (e.g. smoking cessation, control of hypertension and hyperlipidaemia).
- Medicines that may increase the risk of thromboembolism, such as oestrogens and erythropoietic agents, should be used with caution during lenalidomide treatment.
- Appropriate thrombotic prophylaxis medication should be considered during lenalidomide treatment, particularly in patients with multiple thrombotic risk factors, after careful assessment of the balance of risks and benefits in individual patients.
- Treatment with lenalidomide must be discontinued and anticoagulation therapy started in patients who experience thromboembolic events. Once the patient has been stabilised on anticoagulation treatment and any complications of the thromboembolic event have been managed, lenalidomide may be restarted at the original dose, after a reassessment of risks and benefits of treatment. Anticoagulation should then be continued throughout the course of lenalidomide treatment.

Reference:

Drug Safety Update, February 2011, Volume 4, Issue 7, A3, MHRA (www.mhra.gov.uk).

Natalizumab

Risk of progressive multifocal leukoencephalopathy is increased in patients who have had previous immunosuppressant treatment.

UK. The MHRA advised that the risk of developing progressive multifocal leukoencephalopathy (PML) associated with natalizumab is increased in patients who have had previous immunosuppressant therapy. Natalizumab (Tysabri®) is a single disease-modifying therapy for patients with multiple sclerosis who have high disease activity despite treatment with beta-interferon, or who have rapidly evolving severe relapsing remitting disease. PML is a rare, progressive, demyelinating disease of the CNS that may be fatal. The risk of PML increases with treatment duration, especially beyond two years. Natalizumab should be promptly discontinued if PML is suspected, with subsequent appropriate evaluation including standardised MRI and lumbar puncture.

The MHRA explains that a recent analysis of patients diagnosed with PML suggests that the risk of PML is increased in patients who have been treated with an immunosuppressant (e.g. azathioprine, cyclophosphamide, mitoxantrone, and methotrexate) before receiving natalizumab. This analysis used data from an ongoing observational study (Tysabri Global Observational Program in Safety) to compare the risk of PML in patients who were either treated or not treated with immunosuppressants before starting natalizumab.

(See WHO Pharmaceuticals Newsletters No.3, 2010 for the risk of PML in Canada, No.2, 2010 for the risk of PML and IRIS in the UK and the USA as well as No.1, 2010 for recommendations of new measures to minimize the risk of PML in Europe.)

Reference:
Drug Safety Update, March 2011, Volume 4, Issue 8, A2, MHRA (www.mhra.gov.uk).

Omalizumab

Potential risk of arterial thrombotic events

UK. The MHRA warned that use of omalizumab may be associated with an increased risk of arterial thrombotic events. This is based on interim data from an unpublished ongoing observational study and data from controlled clinical trials, where a numerical imbalance of arterial thrombotic events (such as stroke, transient ischaemic attack, myocardial infarction, unstable angina and cardiovascular death (including death from unknown cause)) was observed in association with use of omalizumab. Omalizumab (Xolair) is a monoclonal antibody, which inhibits immunoglobulin E, and is authorized for the treatment of severe persistent allergic asthma in patients aged six years or older in whom standard treatment has failed.

Reference:
Drug Safety Update, February 2011, Volume 4, Issue 7, A4, MHRA (www.mhra.gov.uk).

Seasonal influenza vaccine

Update on spontaneous reporting

New Zealand. Medsafe provided an update on reported adverse events associated with seasonal influenza vaccine. In total, at the end of the season (31 July 2010), CARM (Centre for Adverse Reactions Monitoring) had received 396 reports detailing 936 events. In 2010, three seasonal influenza vaccines were funded by the Ministry of Health: Influvac, Fluvax and Vaxigrip. Over one million doses of vaccine were distributed: 275 000 doses of Influvac; 265 000 doses of Fluvax; with the remainder being Vaxigrip. The distribution of suspected adverse reaction reports was: 197 for Fluvax, 119 for Vaxigrip, 52 for Influvac and 28 brand unknown.

Medsafe says that the most commonly reported suspected reactions following immunization were: fever (131 reports); vomiting (86 reports); injection site inflammation (51 reports); headache (48 reports). There are also reports of rare neurological or immunological conditions that occurred in temporal association with immunization with seasonal flu vaccines. However their causal association cannot be confirmed and may reflect coincidence. CARM received 10 reports of febrile convulsion in children. Of the 10 cases of febrile convulsion, seven were associated with Fluvax, one with Influvac and two were unknown brand. Five of the 10 children who experienced a febrile convulsion had a history of febrile convulsion to previous immunizations. Medsafe states that a crude estimate of the reporting rate of febrile convulsions in New Zealand, in association with Fluvax, did not indicate that the reporting rate of febrile

convulsion was above the expected rate for seasonal influenza vaccines of one case per 1000 doses.

Medsafe and CARM concluded that the nature of the reports was as expected for vaccine adverse events. The reports of febrile convulsions were in line with expected reports for administration of vaccines in children. For the next season in 2011, while the manufacturer of Fluvax is investigating the root cause of the increase in febrile reactions that was observed in Australia in 2010, Fluvax will only be indicated in adults and in children aged five years and above as a precautionary measure.

Reference:

Prescriber Update Vol. 32, No.1 March 2011, (www.medsafe.govt.nz).

WHO Training Course on Pharmacovigilance

New Delhi, 21 to 25 February 2011

Background

A recent survey by WHO (Olsson et al, 2010) identified serious gaps in technical capacity for Pharmacovigilance (PV) in resource limited settings. The Inter-regional Pharmacovigilance Training Course in February 2011, in New Delhi was part of the WHO strategy to help establish at least the minimum standards for PV as identified by WHO and the Global Fund at a consensus meeting in 2010. The course also leveraged lymphatic filariasis as a public health programme that PV centres could liaise with, to share resources across the programmes, to introduce PV within mass preventive treatment campaigns, thereby improving the quality of care and patient safety within such treatment programmes.

The specific objectives of the training course were as follows:

- Raise awareness about public health issues and patient safety in relation to the use of medicines
- Demonstrate the importance of PV activities in improving patient safety and treatment outcomes
- Provide training on the latest tools in basic adverse drug reaction (ADR) reporting, to enhance ADR reporting within countries, and to the WHO Programme for International Drug Monitoring
- Build or reinforce capacity of national PV centres
- Share experiences and challenges faced in establishing or strengthening PV programmes
- Establish networking among regulatory agencies, PV centres, national NTD (neglected tropical diseases) control programmes and WHO for information sharing and providing assistance in detecting signals and making judgments based on sound science.

Two participants per country attended from Cambodia, Lao PDR, Maldives, Nepal and Vietnam, with six participants from India, and represented the national PV centres or the NTD control programmes.

The five-day course covered the following topics:

- WHO Programme for International Drug Monitoring;
- Establishing a PV centre, how to promote reporting;
- Vigibase (a WHO global database of individual case reports), VigiFlow (a web-based case report management system), WHO Adverse Reaction Terminology and WHO Drug Dictionary;
- Causality assessment;
- Collaboration with public health programmes and NTD control programmes in particular;
- Risk management and the prevention of ADRs;
- Rational use of medicines;
- Communication in pharmacovigilance;
- Development of country-specific action plans for next year.

Facilitators included I. Boyd (Australia), A. Viklund and U. Rydberg (Uppsala Monitoring Centre, UMC) and staff from WHO. At the end of the course participants presented draft plans of priority activities for the next 10 months for PV in their settings, with key deliverables, timelines and expected outcomes.

Countries that are not yet members of the WHO Programme (Lao PDR, Maldives) explained their plans to establish a PV centre and join the Programme in the future. Participants from Cambodia, an associate member of the WHO Programme, expressed their intention to become a full member by sending a required number of ADR reports to WHO/UMC. The countries that are members of the WHO Programme (India, Nepal, and Viet Nam) presented their plans to strengthen or expand the current PV work by holding workshops on PV for stakeholders, improving collaboration between PV and public health programmes and other actions. Participants from Nepal and Vietnam confirmed that the course was useful in establishing collaborations, for the first time, between the national PV and the NTD control programmes.

The results of the questionnaire for the evaluation of the training course showed that overall, the meeting was useful for developing or establishing a PV centre within a country and met the participants' expectations and objectives.

Participants will be contacted towards the end of 2011, to follow up on any progress attributable to this course.