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:

Quality Assurance and Safety: Medicines, EMP-HSS,
World Health Organization,
1211 Geneva 27, Switzerland,
E-mail address: pals@who.int

This Newsletter is also available on our Internet website:
http://www.who.int/medicines

Further information on adverse reactions may be obtained from the WHO Collaborating Centre for International Drug Monitoring
Box 1051
751 40 Uppsala
Tel: +46-18-65.60.60
Fax: +46-18-65.60.80
E-mail: info@who-umc.org
Internet: http://www.who-umc.org

Contents

No. 5, 2011

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.

In September, the International Pharmaceutical Federation (FIP) Pharmacy Information Section organized a one-day seminar on pharmacovigilance prior to the FIP's 71st International Congress in Hyderabad. In this issue we include a summary of the seminar.

Printed by the WHO Document Production Services, Geneva, Switzerland

TABLE OF CONTENTS

Regulatory Matters

Safety of medicines

Feature

Aprotinin

The benefits outweigh the risks when it is used as authorized

Canada. Health Canada concluded that the benefits of aprotinin (Trasylol®) outweigh the risks when aprotinin is used as authorized by Health Canada. Aprotinin is authorized for patients undergoing Coronary Artery Bypass Graft (CABG) surgery, also known as heart bypass surgery. The evidence does not suggest an increased risk of death in this use. Health Canada requested that strong warnings, in the form of a Boxed Warning, be added to the prescribing information emphasizing that there have been reports of an increased risk of death in some studies associated with aprotinin use outside of its authorized indication, and that aprotinin should only be used as authorized after careful consideration of the potential benefits and risks. Warnings have also been added emphasizing that physician should adhere to the recommended procedures for the management of blood clotting. Information on the risk of abnormal kidney function has also been added to the Boxed Warning.

Aprotinin marketing was temporarily suspended in November 2007 at Health Canada's request after a clinical trial, the Blood Conservation Using Antifibrinolytics in a Randomized Trial (BART) study. It was stopped due to a higher number of deaths in patients receiving aprotinin relative to two drugs also used to reduce blood loss. The BART study included higher-risk patients undergoing complex cardiac surgeries, a use for which aprotinin and the other two drugs are not authorized in Canada.

Health Canada's decision is based on a comprehensive review of the totality of evidence, which included an evaluation of BART study data, other clinical trial data, post-market studies, and information from Bayer as well as an Expert Advisory Panel on aprotinin that was convened by Health Canada. As a result of this assessment, the manufacturer, Bayer Inc., can resume the marketing of aprotinin in Canada.

(See WHO Pharmaceuticals Newsletter No. 6, 2007 and No. 1, 2008 for temporary market suspension of aprotinin worldwide).

Reference:
Advisories, Warnings and Recalls, Health Canada, 21 September 2011 (*www.hc-sc.gc.ca*).

Asenapine maleate

Serious allergic reactions

USA. The U.S. Food and Drug Administration (US FDA) notified healthcare professionals and patients that serious allergic reactions have been reported with the use of asenapine maleate (Saphris®). The Contraindications, Warnings and Precautions, Adverse Reactions, and Patient Counselling Information sections have been revised to include information about type I hypersensitivity reactions which may include anaphylaxis, angioedema, low blood pressure, rapid heart rate, swollen tongue, difficulty breathing, wheezing, or rash. In several cases, these reactions occurred after the first dose. Asenapine maleate is used to treat symptoms of schizophrenia and bipolar disorder.

The US FDA recommended healthcare professionals to be aware of the risk of hypersensitivity reactions with asenapine maleate and to counsel patients who are receiving the drug about how to recognize the signs and symptoms of a serious allergic reaction. They also recommended that asenapine maleate should not be used in patients with a known hypersensitivity to the drug.

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

Ceftriaxone

The use with calcium containing iv solutions in neonates is contraindicated due to the risk of calcium precipitation

New Zealand. Medsafe (New Zealand Medicines and Medical Devices Safety Authority) announced the updated safety information with the following recommendations:
•ceftriaxone must not be administered simultaneously with calcium-containing intravenous solutions, including continuous calcium-containing infusions via a Y site, because calcium precipitation can occur;
•ceftriaxone is contraindicated in neonates if they require (or are expected to require) treatment with calcium-containing intravenous solutions due to the risk of calcium precipitation;
•in patients over 28 days of age, ceftriaxone and calcium-containing solutions may be administered sequentially to one another if the infusion lines are flushed between infusions with a compatible fluid.

In February 2008, Medsafe advised healthcare professionals that ceftriaxone should not be mixed or administered with calcium-containing solutions due to the risk of precipitation. These recommendations follow Medsafe's review of two *in vitro* studies to assess the potential for precipitation of ceftriaxone and calcium when mixed in infusion lines. The *in vitro* studies were conducted in neonatal and adult plasma; but only showed an increased risk in neonatal plasma.

(See WHO Pharmaceuticals Newsletter No.3, 2009 and No. 4, 2007 for the interaction with calcium containing products in the USA and No.4, 2008 in Canada).

Reference:
Prescriber Update Vol. 32 No. 3, September 2011 (*www.medsafe.govt.nz*).

Citalopram hydrobromide

Abnormal heart rhythms associated with high doses

USA. The US FDA notified healthcare professionals and patients that the antidepressant citalopram hydrobromide (Celexa®) should no longer be used at doses greater than 40 mg per day, because it can cause abnormal changes in the electrical activity of the heart. Changes in the electrical activity of the heart (prolongation of the QT interval of the electrocardiogram [ECG]) can lead to an abnormal heart rhythm (including Torsade de Pointes), which can be fatal. Patients at particular risk for developing prolongation of the QT interval include those with underlying heart conditions and those who are predisposed to low levels of potassium and magnesium in the blood.

According to the US FDA, studies did not show a benefit in the treatment of depression at doses higher than 40 mg per day. Previously, the citalopram drug label stated that certain patients may require a dose of 60 mg per day. The citalopram drug label has been revised to include the new drug dosage and usage recommendations, as well as information about the potential for QT interval prolongation and Torsade de Pointes.

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

Clopidogrel and proton-pump inhibitors

Not all proton pump inhibitors reduce the effectiveness of clopidogrel to the same degree

Canada. Health Canada informed healthcare professionals and patients of updated recommendations involving the use of clopidogrel (Plavix®) in combination with proton pump inhibitors (PPIs). New evidence has shown that while PPIs do interact with clopidogrel, not all reduce the effectiveness of clopidogrel to the same degree.

In 2009, the labelling for clopidogrel was updated to indicate that the use of any PPI in patients taking clopidogrel should be discouraged, as emerging data suggested that PPIs potentially reduced the ability of clopidogrel to protect against blood clots.
Since that time, new studies have shown that, while PPIs do interact with clopidogrel, not all PPIs interact to the same degree: some have a strong effect on clopidogrel, while others do not.

The labelling for clopidogrel has been updated with new recommendations regarding the use of PPIs:
•PPIs known to strongly or moderately reduce clopidogrel effectiveness should be avoided. Omeprazole is one of these;
•if a PPI must be used in a patient taking clopidogrel, consider a PPI that does not interact as strongly. Pantoprazole is one of these.

Patients taking Plavix should continue taking it as directed and should talk to their health professional regarding any questions or concerns about their treatment. There are alternatives to PPIs for the treatment of stomach ulcers and heartburn.

(See WHO Pharmaceuticals Newsletter No. 2 and No. 3, 2010 for interactions in Europe, New Zealand, the USA and the UK).

Reference:
Advisories, Warnings and Recalls, Health Canada, 22 September 2011 (*www.hc-sc.gc.ca*).

Dasatinib

Safety information regarding pulmonary arterial hypertension

Canada. Health Canada announced Bristol-Myers Squibb Canada's (BMS) new safety information regarding reports of serious pulmonary arterial hypertension (PAH) in patients treated with dasatinib (Sprycel®).

PAH, a subtype of pulmonary hypertension (PH), is a rare,

severe and progressive disease with no apparent cause, characterized by vascular proliferation and remodelling of the small pulmonary arteries, leading to increased pulmonary artery pressure and vascular resistance. PAH is diagnosed by right heart catheterization and defined by haemodynamic criteria including a mean pulmonary arterial pressure of 25 mmHg or higher and pulmonary capillary wedge pressure of 15 mmHg or lower (pre-capillary PH in the absence of post-capillary PH).

A total of 60 serious PH cases have been reported worldwide, between June 2006 and June 2011, including 12 cases of pulmonary arterial hypertension (PAH) confirmed by right heart catheterization, in association with dasatinib treatment.

Some patients diagnosed with PAH during dasatinib therapy were taking concomitant medications or had co-morbidities in addition to the underlying malignancy.

It is recommended that:
- patients should be evaluated for signs and symptoms of underlying cardiopulmonary disease before initiating dasatinib therapy;
- patients who develop symptoms suggestive of PAH such as dyspnea and fatigue after initiation of treatment with dasatinib should be evaluated for more common etiologies and treatment should be withheld during evaluation, if symptoms are severe;
- the diagnosis of PAH should be considered if no alternative diagnosis can be found;
- Dasatinib should be permanently discontinued if the diagnosis of PAH is confirmed.

It is also informed that improvements in hemodynamic and clinical parameters have been observed in patients with PAH following cessation of dasatinib therapy.

Reference:
Advisories, Warnings and Recalls, Health Canada, 30 August 2011 (www.hc-sc.gc.ca).

Dronedarone

Information on increase in cardiovascular events in patients with permanent atrial fibrillation

Canada(1). Health Canada announced that Sanofi-aventis Canada Inc. informed new safety information regarding dronedarone (Multaq®):

- Dronedarone should be prescribed only in patients with a history of, or current non-permanent atrial fibrillation (AF) to reduce the risk of cardiovascular hospitalization due to AF;
- Dronedarone must not be prescribed in patients with permanent AF (duration for at least six months or duration unknown), and in whom an attempt to restore sinus rhythm is no longer considered;
- it is recommended to closely monitor patients taking dronedarone. If patients treated with dronedarone develop permanent AF, treatment with dronedarone should be discontinued.

Contraindications, warnings and precautions in the current Product Monograph should be followed. In relation to cardiovascular risk the following are particularly relevant:

- Dronedarone is contraindicated in patients with:
  - severe congestive heart failure (Stage NYHA IV) and other unstable haemodynamic conditions
  - Bradycardia < 50 bpm;
- Dronedarone should be used with caution in patients with moderate congestive heart failure (Stage NYHA III) and only if the benefits are deemed to outweigh the risks involved;
- if heart failure develops or worsens, consider the suspension or discontinuation of dronedarone.

Dronedarone is authorized for the treatment of patients with a history of, or current AF to reduce the risk of cardiovascular hospitalization due to AF.

Europe(2). The European Medicines Agency (EMA)'s Committee for Medicinal Products for Human Use (CHMP) has recommended restricting the use of dronedarone (Multaq®). The Committee also recommended a number of other risk minimization measures to reduce the risk of injuries to liver, lung and cardiovascular system. Patients who are currently taking dronedarone are also recommended to have their treatment evaluated by their doctor at their next scheduled appointment.

The review of the overall balance of benefits and risks of dronedarone was initiated in January 2011 because of reports of severe liver injury in patients treated with the medicine. On the basis of the evaluation of currently available data, the Committee concluded that:
- treatment with dronedarone should be restricted to patients with paroxysmal or persistent atrial fibrillation when sinus rhythm has been obtained. It is no longer indicated for use in patients when atrial fibrillation is still present;
- treatment with dronedarone should only be started and monitored by a specialist

after other anti-arrhythmic medicines have been considered;
- Dronedarone must not be used in patients with permanent atrial fibrillation, heart failure or left ventricular systolic dysfunction (impairment of the left side of the heart);
- doctors should consider discontinuation of treatment if atrial fibrillation re-occurs;
- Dronedarone must not be used in patients who have had previous liver or lung injury following treatment with amiodarone, another anti-arrhythmic medicine;
- patients on dronedarone should have their lung and liver function as well as their heart rhythm regularly monitored. Especially the liver function should be closely monitored during the first few weeks of treatment.

The Committee's opinion has been forwarded to the European Commission for the adoption of a decision.

(See WHO Pharmaceuticals Newsletter No. 4, 2011 for increased risk of death or serious cardiovascular events in Canada and the USA).

Reference:
(1) Advisories, Warnings and Recalls, Health Canada, 4 August 2011 (www.hc-sc.gc.ca).
(2) Press release, EMA, 22 September 2011 (www.ema.europa.eu).

Finasteride

Potential rare risk of breast cancer in men

Canada. Health Canada is informing healthcare practitioners and patients of a labelling update for finasteride that includes information on rare reports of breast cancer in men. The labelling for finasteride products has already been updated to include information on the potential risk of male breast cancer. Health Canada recommended patients taking finasteride to report any changes in their breasts to their doctor. Changes might include breast enlargement, lumps, tenderness, pain or nipple discharge.

Male breast cancer has been reported in a small number of patients worldwide with both the 1 mg and 5 mg formulations of finasteride. Most of the reports have been in association with the 5 mg formulation. Based on the currently available evidence, it is not known with certainty whether finasteride can cause breast cancer, nor can this possibility be ruled out at this point in time.

(See WHO Pharmaceuticals Newsletter No. 1, 2010 for potential risk of male breast cancer in the UK).

Reports in WHO Global ICSR database, Vigibase:

Finasteride

Number of reports: 429 (SOC Neoplasm, Male)

Most reported reactions (number of events):

Carcinoma:	*83*
Neoplasm NOS:	*74*
Pulmonary carcinoma:	*40*
Genital neoplasm malignant male:	*39*
Gastric carcinoma:	*27*
Breast neoplasm male:	*21*
Bladder carcinoma	*16*
Leukaemia	*12*

Reference:
Advisories, Warnings and Recalls, Health Canada, 4 August 2011 (www.hc-sc.gc.ca).

Fluconazole

Long-term, high-dose use during pregnancy may be associated with birth defects

USA. The US FDA announced to the public that treatment with chronic, high doses (400-800 mg/day) of fluconazole (Diflucan®) during the first trimester of pregnancy may be associated with a rare and distinct set of birth defects in infants. This risk does not appear to be associated with a single, low dose of fluconazole 150 mg to treat vaginal yeast infection (candidiasis). Based on this information, the US FDA changed the pregnancy category for fluconazole indications (other than vaginal candidiasis) from category C to category D. Pregnancy category D means there is positive evidence of human fetal risk based on human data but the potential benefits from use of the drug in pregnant women with serious or life-threatening conditions may be acceptable despite its risks. The pregnancy category for a single, low dose of fluconazole has not changed and remains category C.

The US FDA recommends that healthcare professionals should counsel patients if the drug is used during pregnancy or if a patient becomes pregnant while taking the drug; patients should notify their healthcare professionals if they are or become pregnant while taking fluconazole. If a patient uses fluconazole during pregnancy, the patient should be informed of the potential risk to the fetus.

Reports in WHO Global ICSR database, Vigibase:

Fluconazole

Number of reports: 149 (SOC Foetal Disorders)

Most reported reactions (number of events):

Abortion:	*39*
Drug exposure in pregnancy:	*36*
Congenital anomaly NOS:	*14*
Death foetal:	*11*
Cleft palate:	*8*
Malformations multiple:	*7*
Malformation skull:	*7*
Face malformation:	*7*

Reference:
FDA Drug Safety Communication, US FDA 3 August 2011 (*www.fda.gov*).

Fusidic acid and Statins

A strict warning against concomitant use with statins: risk of rhabdomyolysis

UK. The Medicines and Healthcare products Regulatory Agency (MHRA) announced that product information for systemic fusidic acid (Fucidin®) is being updated to include a strict warning against concomitant use with statins because of a risk of serious and potentially fatal rhabdomyolysis. The MHRA advised that healthcare professionals should be aware of strengthened warnings regarding this potential drug interaction.

Fusidic acid and its salts (including sodium fusidate) are antistaphylococcal agents that are used in the treatment of serious or deep-seated infections requiring good tissue or bone penetration, such as osteomyelitis. Systemic formulations include tablets, suspension, and intravenous infusion.

It has been known for some time that there is an increased risk of rhabdomyolysis when systemic fusidic acid is used at the same time as some statins. The product information for systemic fusidic acid and for simvastatin and atorvastatin lists this interaction and warns of the associated risk.

According to the MHRA, in recent years, the number and severity of case reports of rhabdomyolysis (including those with a fatal outcome) suspected to be due to an interaction between fusidic acid and a statin have increased.

The MHRA also advised healthcare professionals that:
- in patients for whom the use of systemic fusidic acid is essential, statin treatment should be temporarily discontinued throughout the duration of fusidic acid treatment;
- to ensure clearance of systemic fusidic acid, statin therapy may be reintroduced seven days after the last dose of systemic fusidic acid;
- in exceptional cases where prolonged systemic fusidic acid treatment is necessary, the need for co-administration of a statin should be considered on an individual basis and only under close medical supervision;
- patients should be clearly advised to seek medical advice immediately if they experience any symptoms of muscle weakness, pain, or tenderness;
- any muscle symptoms reported in patients who are prescribed statins should be followed up.

Reference:
Drug Safety Update, July 2011, Volume 5, issue 2, A1, MHRA, (*www.mhra.gov.uk*).

Gonadotropin-releasing hormone agonists

Heart-related risk in men treated for prostate cancer

Canada. Health Canada informed healthcare professionals and patients about a possible increased risk of certain heart-related events in men being treated for prostate cancer with a type of prescription drug known as a Gonadotropin-Releasing Hormone (GnRH) agonist. The labelling for GnRH agonist drugs has been updated to add a warning on the potential increased risk of heart-related side effects. There have been reports of heart attacks, stroke and heart-related deaths in patients treated with GnRH agonists for prostate cancer. Based on information collected from scientific literature, the risk appears to be low.

GnRH agonists work by reducing or suppressing male hormones (androgens, such as testosterone), which in turn leads to shrinkage of prostate tumours or slowing of the growth of prostate cancer. This therapy belongs to a category of therapies known as Androgen Deprivation Therapy. GnRH agonist drugs used in the treatment of prostate cancer currently marketed in Canada are leuprolide acetate (Eligard®), leuprolide acetate (Lupron®), buserelin acetate (Suprefact®), triptorelin pamoate (Trelstar®), histrelin acetate (Vantas®) and goserelin acetate (Zoladex®).

Health Canada recommends that patients taking a GnRH agonist drug should talk to their healthcare professional if they have a history of heart disease or heart disorders, or if they have any questions or concerns regarding their prostate cancer treatment and that patients should not stop taking a GnRH agonist drug without first talking to their healthcare professional. Health Canada also recommends

patients to tell their doctor if they have diabetes, heart disease, a previous heart attack or stroke, or any cardiovascular risk factors like high blood pressure, high cholesterol, or cigarette smoking before starting treatment with a GnRH agonist.

When determining an appropriate prostate cancer treatment, physicians should weigh the benefits of Androgen Deprivation Therapy against the potential cardiovascular risk of GnRH agonists, along with any additional factors that may put a patient at increased risk for heart-related events. Patients receiving a GnRH agonist should be monitored for signs and symptoms suggestive of development of cardiovascular disease, and managed according to current clinical practice.

Reference:
Advisories, Warnings and Recalls, Health Canada, 8 September 2011 (*www.hc-sc.gc.ca*).

Isotretinoin

Risk of depression – inform and monitor

New Zealand. Medsafe reminds prescribers that all patients treated with isotretinoin need to be informed of the risk of depression and/or suicidal ideation and be monitored for the development of depression during treatment. Medsafe also notes that patients should be asked to seek medical advice immediately if these symptoms occur even after isotretinoin has been discontinued.

Isotretinoin is approved for use in the treatment of severe forms of nodulo-cystic acne that are resistant to other treatment. Isotretinoin should only be prescribed by prescribers who are experienced in the use of isotretinoin and understand the risk of teratogenicity.

An association between the use of isotretinoin and the development of depression and/or suicidal ideation was first identified from case reports and published case series. Subsequent epidemiological studies have reported conflicting results. In many cases, confounding factors such as the high prevalence of psychiatric morbidity in adolescents and patients with acne are present and make causality assessment difficult.

A recent study conducted in New Zealand found that mood change occurred in 5-10% of patients taking isotretinoin with the incidence increasing with larger doses. A recent Swedish cohort study reported a positive association between the use of isotretinoin and suicide attempts. This study found that the risk began to increase two years before starting isotretinoin and peaked six months after stopping treatment. In addition the risk was greatest in patients receiving repeated courses of isotretinoin, suggesting it might be related to the patients' perception of their underlying acne.

(See WHO Pharmaceuticals Newsletter No. 3, 2005 for reports of suicidal thoughts in Australia.)

Reference:
Prescriber Update Vol. 32 No. 3, September 2011 (*www.medsafe.govt.nz*).

Lenalidomide

The risk of new cancers but benefit-risk balance remains positive

Europe. The EMA confirmed that the benefit-risk balance for lenalidomide (Revlimid®) remains positive within its approved patient population but advises doctors of the risk of new cancers as a result of treatment with the medicine.

Lenalidomide was reviewed following the results of three new studies showing a higher rate of new cancers in patients with newly diagnosed multiple myeloma who were being treated with lenalidomide and received other treatments concomitantly. The studies showed a four-fold increase in the number of new cancers in patients being treated with lenalidomide, including solid tumours and cancers of the blood and the immune system.

The Committee reviewed all available data on new cancers in the approved population, including data from studies and post-marketing data. The Committee concluded that the benefits of lenalidomide, particularly improved survival, continue to outweigh the risks but recommended that the prescribing information for lenalidomide be updated with a warning and advice to doctors on the risk of new cancers.

The Committee's conclusion does not cover its use outside of the current authorized indication. The Committee's opinion has now been forwarded to the European Commission for the adoption of a decision.

(See WHO Pharmaceuticals Newsletter No. 3, 2011 for Investigation of risk of second primary malignancies in myeloma in the UK).

Reports in WHO Global ICSR database, Vigibase:

Lenalidomide

Number of reports: 149 (SOC Neoplasm)

Most reported reactions (number of events):

Myelomatosis multiple:	*1415*
Leukaemia granulocytic:	*186*
Leukaemia acute:	*70*
Leukaemia lymphocytic:	*64*
Leukaemia:	*43*
Neoplasm malignant:	*31*
Non-Hodgkin's lymphoma:	*30*
Pulmonary carcinoma:	*29*
Lymphoma malignant:	*23*
Thrombocythaemia:	*20*
Skin neoplasm malignant:	*20*

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

Terpenic-based anti-cough medicines

Contraindications for use in children under 30 months, children with a history of febrile convulsion or epilepsy and children with a recent history of anorectal lesion

Europe. The EMA recommended updating the product information for suppositories containing terpenic derivatives with new contraindications following the finalization of a review of their use in children under 30 months by the CHMP. The Committee concluded that there was a risk of these medicines inducing neurological disorders, especially convulsions, in infants and small children and recommended that their use should be contraindicated in children under 30 months and in children with a history of epilepsy or febrile convulsion. It also concluded that there was a risk of these medicines causing local anorectal lesions (precancerous growths in the anus or rectum) and recommended their use should be contraindicated in children with a recent history of anorectal lesion.

Suppositories containing terpenic derivatives (including camphor, cineole, niaouli, wild thyme, terpineol, terpine, citral, menthol and essential oils of pine needle, eucalyptus and turpentine) are typically indicated for supportive treatment for mild acute bronchial disorders, particularly productive and non-productive cough.

The review procedure was initiated after the French medicines agency expressed concerns about the safety of suppositories containing terpenic derivatives, particularly the risk of serious neurological side effects such as convulsions in young children. The Committee's opinion has now been forwarded to the European Commission for the adoption of a decision.

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

Tumour Necrosis Factor-alpha Blockers

Boxed Warning updated for risk of infection from *Legionella* and *Listeria*

USA. The US FDA notified healthcare professionals that the Boxed Warning for the entire class of Tumor Necrosis Factor-alpha (TNFα) blockers including infliximab (Remicade®), etanercept (Enbrel®), adalimumab (Humira®), certolizumab pegol (Cimzia®), and golimumab (Simponi®) has been updated to include the risk of infection from two bacterial pathogens, *Legionella* and *Listeria*. In addition, the Boxed Warning and Warnings and Precautions sections of the labels for all of the TNFα blockers have been revised so that they contain consistent information about the risk for serious infections and the associated disease-causing pathogens. Patients treated with TNFα blockers are at increased risk for developing serious infections involving multiple organ systems and sites that may lead to hospitalization or death due to bacterial, mycobacterial, fungal, viral, parasitic, and other opportunistic pathogens.

The class of TNFα blockers are used to treat Crohn's disease, ulcerative colitis, rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, plaque psoriasis, and/or juvenile idiopathic arthritis.

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

Zoledronic acid

New contraindication and updated warning on kidney impairment

USA. The US FDA notified healthcare professionals and patients of an update to the drug label for zoledronic acid (Reclast®) regarding the risk of kidney failure. Cases of acute renal failure requiring dialysis or having a fatal outcome following zoledronic acid use have been reported to the US FDA. The revised label states that zoledronic acid is contraindicated in patients with creatinine clearance less than 35 mL/min or in patients with evidence of acute renal impairment. The label also recommends that healthcare professionals screen patients prior to administering zoledronic acid in order to identify at-risk patients. Healthcare professionals are also recommended to monitor

renal function in patients who are receiving zoledronic acid.

The Reclast® Medication Guide for patients is being updated to contain information about the risk of severe kidney problems. In addition, the manufacturer will issue a Dear Healthcare Provider letter to inform healthcare professionals about this risk.

These labelling changes are being made to the Reclast® label only, although zoledronic acid, also sold as Zometa®, is approved for treatment of cancer-related indications. Renal toxicity is already addressed in the Warnings and Precautions section of the Zometa® as well as in the Reclast® label. Dose reductions for Zometa® are provided for patients with renal impairment.

(See WHO Pharmaceuticals Newsletter No. 3, 4 and 6, 2010 for adverse effects on renal function in the UK, New Zealand and Canada).

Reference:

FDA Drug Safety Communication, US FDA, 1 September 2011 (*www.fda.gov*).

Bevacizumab

Premature ovarian failure

New Zealand. Medsafe advised prescribers to discuss the possibility of ovarian failure with all female patients prior to treatment with bevacizumab (Avastin®) and that patients should also be monitored for the development of signs and symptoms of ovarian failure during treatment.

This advice follows the publication of a recent study, NSABP-C08, which found ovarian failure occurs commonly in association with bevacizumab use. Although ovarian failure is a well recognized complication of chemotherapy, it has not previously been reported in clinical trials of bevacizumab.

Bevacizumab is a recombinant monoclonal antibody that inhibits tumour angiogenesis and tumour growth. Bevacizumab is approved for use in New Zealand for the treatment of various cancers including colorectal cancer, renal cell cancer, non-squamous non-small cell lung cancer, breast cancer, and high grade malignant glioma.

Patients with ovarian failure usually present with amenorrhoea (or irregular menses) with or without symptoms of oestrogen deficiency (such as hot flushes, night sweats, and emotional lability). Medical intervention may be required for symptom control and to prevent the long term consequences of oestrogen deficiency, such as osteoporosis.

Reference:
Prescriber Update Vol. 32 No. 3, September 2011 (*www.medsafe.govt.nz*).

Bisphosphonates

Rare but serious ocular inflammatory effects

New Zealand. Medsafe reminded prescribers that bisphosphonates have been associated with a number of rare but serious ocular inflammatory effects, including uveitis and scleritis.

As of 30 June 2011, the Centre for Adverse Reactions Monitoring (CARM) had received a total of 28 reports of uveitis (including iritis) associated with a variety of medicines. Of these reports over one third (8) were assessed by CARM as being causally associated with the use of bisphosphonates. Alendronate was associated with the majority of the reports received (4); reports of uveitis have also been received in association with the use of pamidronate (3) and zoledronate (1). Due to the indications for which bisphosphonates are approved, the cases generally involved older females.

Time to onset of the reaction after bisphosphonate administration was generally short, with all cases occurring within one month of treatment initiation. The majority of cases noted that the patient had recovered or improved at the time of the report.

Uveitis is characterised by inflammation of the uvea – the pigmented, vascular inner coat of the eye consisting of the choroid, ciliary body and iris. The most common symptoms of uveitis include redness of the eye (particularly around the margin of the cornea), photophobia, eye pain (typically an ache), decreased or blurred vision, and floating spots in the visual field. Uveitis can affect one or both eyes. Serious complications of uveitis include cataracts, glaucoma, retinal oedema and permanent blindness.

In patients with suspected drug-induced uveitis the suspected medicine should be discontinued and the patient referred to an ophthalmologist for examination and treatment to control the inflammation. With prompt diagnosis and treatment, drug-induced uveitis is almost always reversible.

Reference:
Prescriber Update Vol. 32 No. 3, September 2011 (*www.medsafe.govt.nz*).

Drospirenone-containing combined oral contraceptives

Possible Increased Risk of Blood Clots

USA. The US FDA announced that the agency has not yet reached a conclusion, but remains concerned, about the potential increased risk of blood clots with the use of drospirenone-containing birth control pills.

The US FDA has completed its review of the two 2011 studies that evaluated the risk of blood clots for women who use drospirenone-containing birth control pills and is continuing its review of a separate FDA-funded study that evaluated the risk of blood clots in users of several different hormonal birth control products (contraceptives). Preliminary results of the FDA-funded study suggest an approximately 1.5-fold increase in the risk of blood clots for women who use drospirenone-containing birth control pills compared to users of other hormonal contraceptives.

Given the conflicting nature of the findings from six published

studies evaluating this risk, as well as the preliminary data from the FDA-funded study, FDA has scheduled a joint meeting of the Reproductive Health Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee on 8 December 2011 to discuss the risks and benefits and specifically the risk of blood clots of drospirenone-containing birth control pills.

(See WHO Pharmaceuticals Newsletter No.3, 2010 for update on the risk of venous thromboembolism in the UK and No.4, 2011 in the USA and in the UK).

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

Gadolinium based contrast agents

Risk of Nephrogenic Systemic Fibrosis

New Zealand. Medsafe reminded prescribers of a rare but severe side effect associated with gadolinium based contrast agents (GBCA), often used during MRI. This reminder follows a recent publication that describes five cases of Nephrogenic Systemic Fibrosis (NSF) associated with the use of gadodiamide (Omniscan®) in New Zealand. Medsafe advised healthcare professionals that (i) all patients should be screened for renal dysfunction prior to receiving a GBCA, (ii) gadodiamide and gadopentetic acid (Magnevist®) are contraindicated for use in patients with severe renal insufficiency (GFR < 30 mL/min/1.73m^2) and for use in patients with acute renal insufficiency of any severity due to the hepato-renal syndrome, or in the perioperative liver transplantation period, (iii) other GBCAs should be used with caution in patients with severe renal insufficiency. However, the minimum recommended dose should be used and sufficient time should be allowed between doses to ensure complete elimination.

A review by the European Medicines Agency in 2010 concluded that GBCAs are associated with varying degrees of risk of developing NSF. This difference appears to be related to their ability to release free gadolinium ions into the circulation.
According to Medsafe, using the European classification, the GBCAs approved for use in New Zealand can be placed in the following risk categories:

- high risk: gadodiamide (Omniscan®), gadopentetic acid (Magnevist®);
- medium risk: gadobenic acid (Multihance®);
- Low risk: gadobutrol (Gadovist®), gadoteric acid (Dotarem®).

NSF is a very rare systemic disease characterized by thickening and hardening of the skin with fibrosis of the dermis. It can also affect other organs such as the lungs and the heart.

NSF presents with pain, pruritis, joint stiffness, tightness, swelling of the hands and feet, paraesthesias and burning. Dry skin, weakness and warmth can also occur. Skin findings can be localized or generalized and the distribution is often symmetric and bilateral. Although the progression of NSF can be unpredictable, all patients eventually develop limitation of movement. In some cases the disease is fatal. Although a number of treatments have been proposed, there is currently no single effective treatment for NSF.

(See WHO Pharmaceuticals Newsletter No.1, 2010 for the risk of nephrogenic systemic fibrosis in Europe, No.1, 2010 in Australia and No.3, 2007 in the USA).

Reference:
Prescriber Update Vol. 32 No. 3, September 2011 (*www.medsafe.govt.nz*).

Ondansetron

Risk of abnormal heart rhythms

USA. The US FDA notified healthcare professionals and patients of an ongoing safety review and labelling changes for ondansetron (Zofran®), including ondansetron hydrochloride and generics, to include a warning to avoid use in patients with congenital long QT syndrome because these patients are at particular risk for Torsade de Points. Recommendations for ECG monitoring in patients with electrolyte abnormalities (e.g., hypokalemia or hypomagnesemia), congestive heart failure, bradyarrhythmias, or in patients taking other medications that can lead to QT prolongation, are being included in the labels.

Ondansetron may increase the risk of developing prolongation of the QT interval of the electrocardiogram, which can lead to an abnormal and potentially fatal heart rhythm, including Torsade de Pointes. Patients at particular risk for developing Torsade de Pointes include those with underlying heart conditions, such as congenital long QT syndrome, those who are predisposed to low levels of potassium and magnesium in the blood, and those taking other medications that lead to QT prolongation.

Ondansetron is in a class of medications called 5-HT_3 receptor antagonists. It is used to prevent nausea and vomiting caused by cancer chemotherapy, radiation therapy and surgery. The US FDA is requiring GlaxoSmithKline to conduct a thorough QT study to determine the degree to which ondansetron may cause QT interval prolongation.

Reference:
FDA Drug Safety Communication, US FDA, 15 September 2011 (*www.fda.gov*).

Proton pump inhibitors

Reports of acute renal reactions, primarily interstitial nephritis

New Zealand. Medsafe announced that the Centre for Adverse Reactions Monitoring (CARM) continued to receive reports of acute renal reactions, primarily interstitial nephritis, in association with the use of proton pump inhibitors (PPIs).

As of 30 June 2011, CARM had received a total of 65 reports of interstitial nephritis associated with omeprazole (62) and pantoprazole (3). The limited use of lansoprazole and esomeprazole in New Zealand may explain the lack of reports to CARM for these PPIs.

Patients with acute interstitial nephritis can present with the non-specific symptoms consistent with acute renal failure. Presenting symptoms include fever, rash, eosinophilia, malaise, myalgia, arthlargia, weight loss, altered urine output, blood or pus cells in the urine and/or high blood pressure. In some cases symptoms may also mimic those of vasculitis.

In patients presenting with symptoms suggestive of interstitial nephritis the involvement of PPIs should be considered among a number of other risk factors. Other risk factors include: the use of β-lactams, NSAIDs, sulfonamides and diuretics; the presence of infection; and immune and neoplastic disorders.

A definitive diagnosis of interstitial nephritis can only be confirmed with renal biopsy. If interstitial nephritis is suspected, urine microscopy and renal function should be assessed.

In cases of medicine-induced interstitial nephritis, the offending agent should be discontinued immediately and the patient referred to a renal physician for further assessment.

(See WHO Pharmaceuticals Newsletter No.4, 2006 for reports of interstitial nephritis in New Zealand).

Reference:
Prescriber Update Vol. 32 No. 3, September 2011 (*www.medsafe.govt.nz*).

Quinine

Off-label use of quinine for the treatment of nocturnal cramps and thrombocytopenia

Australia. The Therapeutic Goods Administration (TGA) reported that the TGA continues to receive reports of thrombocytopenia in people taking quinine to treat muscle cramps. The TGA reminded healthcare professionals that quinine is not approved for the treatment of nocturnal cramps because of its low efficacy and the risk of thrombocytopenia. Non-pharmacological interventions, such as stretching, should be considered for preventing cramps.

In 2004, the Product Information (PI) for quinine tablets was amended and the indication for nocturnal cramps removed. Quinine tablets are now only approved for treatment of malaria due to strains of Plasmodium falciparum resistant to chloroquine and the related 4-aminoquinolines.

Up to 2004, the TGA had received 228 reports of thrombocytopenia in people taking quinine, six of which were fatal. Since 2004, the TGA has received a further 21 reports of thrombocytopenia in people taking quinine, including several in the past few years. In most cases, patients were prescribed quinine to treat leg cramps.

According to the TGA, utilization data show that although prescribing of quinine has reduced substantially since removal of the indication and listing for muscle cramps, private prescribing of quinine continues. It is likely that 'off-label' prescribing for muscle cramps occurs.

(See WHO Pharmaceuticals Newsletter No.1, 2011, No.4, 2010 and No.1, 2007 for off-label use in treating leg cramps in the USA, UK and New Zealand).

Reference:
Medicines Safety Update Vol 2, No 4, August 2011 (www.tga.gov.au).

Uromitexan

Association of uromitexan, multi-dose vials with fatal gasping syndrome in neonates and infants

Canada. Health Canada announced that Baxter Corporation informed healthcare professionals of the risk of fatal gasping syndrome in neonates and infants associated with the use of uromitexan (Mesna®) multi-dose vials and advised that the new multi-dose vials of uromitexan contain benzyl alcohol and is only indicated for use in adults and children 13 years and older.

Neonatal gasping syndrome is characterized by severe metabolic acidosis, gasping respirations, progressive hypotension, seizures, central nervous system depression, intraventricular haemorrhage, and death in preterm, low-birth weight infants.

The preservative benzyl alcohol can cause serious or fatal reactions in neonates and infants, and can also cause adverse events in older paediatric patients. Cases of neonatal 'gasping syndrome' have been reported in association with the intravenous administration of products containing benzyl alcohol as preservative.

The Product Monograph for uromitexan multi-dose vials contains a warning box about the potential risk of fatality in neonates and infants due to the benzyl alcohol content of the multi-dose vials. In addition, the Precautions-Use in children section has been updated to specify this risk.

Reference:
Advisories, Warnings and Recalls, Health Canada, 6 September 2011 (*www.hc-sc.gc.ca*).

Venlafaxine

Published case reports suggest an association with stress cardiomyopathy

Australia. According to the TGA , published case reports suggest that stress cardiomyopathy may be an adverse effect of venlafaxine. There is currently insufficient evidence to confirm an association, although a biologically plausible mechanism exists. TGA reminded clinicians to report suspected adverse reactions of all types, even for drugs that have been available for many years.

Venlafaxine is a potent selective serotonin-noradrenaline reuptake inhibitor. It also exhibits rate-dependent sodium channel blocking activity. Venlafaxine is approved for the treatment of major depression, generalized anxiety disorder, social anxiety disorder and panic disorder, including prevention of relapse.

The product information states that venlafaxine causes a dose-related increase in resting heart rate and is associated with hypertension and increased serum cholesterol, which are presumed to be additive to other cardiovascular risk factors, and that venlafaxine should be used with caution in patients with unstable heart disease. In these patients, assessment of the cardiovascular system (e.g. ECG, serum electrolytes during diuretic treatment) should be considered during treatment with venlafaxine, particularly when the dose is increased beyond 150–200 mg daily.

The TGA continues to monitor the potential association between venlafaxine and stress cardiomyopathy.

Reference:
Medicines Safety Update Vol 2, No 4, August 2011 (www.tga.gov.au).

FIP pharmacovigilance seminar in India

Mr Graeme Vernon, Senior Drug Information Pharmacist, Austin Health, Melbourne, Australia; Executive Committee, FIP Pharmacy Information Section

The International Pharmaceutical Federation (FIP) held its 71st International Congress in Hyderabad in September 2011. Prior to the congress, the FIP Pharmacy Information Section organized a one-day seminar entitled "Pharmacovigilance and Medicines Information to Enhance Patient Safety".

The annual Congress provides an opportunity for pharmacists from a diverse range of countries to discuss issues of global importance. The seminar had a focus on India and the role of pharmacists in improving patient safety. The speakers were:

- Alex Dodoo, Head, UMC-Africa; WHO Collaborating Centre for Advocacy and Training in Pharmacovigilance, Accra, Ghana;
- Paul Lalvani, Dean and Director, Empower School of Health, New Delhi, India;
- Sten Olsson, Chief WHO Programme Officer, Uppsala Monitoring Centre;
- Shanthi Pal, Pharmacovigilance Programme Manager, Quality Assurance and Safety: Medicines, WHO;
- Graeme Vernon, Drug Information Pharmacist, Austin Health, Melbourne, Australia.

This was the fourth pharmacovigilance meeting organized by the Pharmacy Information Section. Previous meetings were held in Cairo (2005), Salvador de Bahia (2006) and Beijing (2007).

The seminar aimed to link the clinical role of pharmacists managing adverse drug reactions with local and international pharmacovigilance responsibilities. It also covered factors which can lead to medication errors, and how to change systems to improve safety.

This was an opportunity to emphasize the extended scope of pharmacovigilance which now includes:

- adverse effects;
- patient effects of inadequate product quality, including unexpected lack of efficacy;
- patient effects of inadequate use (including medication errors, dependence and abuse, and poisoning);
- safety challenges of mass treatment campaigns such as immunization programs and other public health programs.

It is difficult for many pharmacists to understand the global dimensions of pharmacovigilance. Therefore, the scope of the WHO Programme for International Drug Monitoring was explained and how WHO works with the national centres and its collaborating centres in Uppsala and Accra. WHO develops relevant policies, norms, standards and guidelines for pharmacovigilance. The Uppsala centre collects and analyses reports from all global sources, communicates potential safety issues, and provides support and training for pharmacovigilance programs. The Accra centre provides ground and country level support and focuses on public health programs. Although it has a strong presence in Africa its activities extend to other countries where support is required.

In recent years WHO pharmacovigilance activities have become more patient centred. The traditional approach has been on problems relating to medicines but the overall aim is to minimize harm to patients. Current systems can be complemented by a public health perspective which rapidly addresses key safety issues, provides rates of adverse effects, monitoring of adverse effects in special populations (e.g. children) and supporting risk management plans.

The various challenges confronting pharmacovigilance were outlined. The level of spontaneous reporting by health professionals remains low compared to its potential, the level of clinical details provided limits the interpretation of the event, and delays in processing and forwarding reports can impair the process to identify signals.

Cohort event monitoring is being developed as an alternative to spontaneous reporting. This involves prospectively checking for adverse events in a defined population before and after the mass deployment of a new drug, or for new drugs introduced with safety concerns. Cohort monitoring aims to:

- characterize known reactions and identify signals for unrecognised reactions and interactions;
- measure risks and identify risk factors;

- provide utilization data;
- assess safety in pregnancy and lactation;
- detect inefficacy.

Current cohort monitoring programs are following antimalarials and antiretrovirals in a number of countries. Targeted spontaneous reporting is another approach where a particular treatment is followed in detail as part of routine care. Where facilities are available, electronic longitudinal surveillance can link and follow prescribing with patient outcomes. This approach can characterize the duration of adverse effects after onset and distinguish transient effects from those which persist during continuing drug exposure.

Initiatives to improve the level of pharmacovigilance in India were outlined. While the national pharmacovigilance program was launched in 2004, there has been a major effort to enhance and co-ordinate activity since 2010. Current plans are for a National Co-ordinating Centre, 40 reporting centres, and four zonal offices (to provide operational and logistic support). Focused adverse reaction monitoring is proposed for drugs or vaccines which have safety concerns of particular relevance to India.

There has been a trend for pharmaceutical manufacturers to outsource their pharmacovigilance operations to India. This is attractive partly because of the variation between the requirements for mandatory monitoring in different countries. Indian companies specializing in pharmacovigilance can provide the skills and technology required and are familiar with global pharmacovigilance requirements because of the export focus of the industry.

For the clinical pharmacist, pharmacovigilance is as much about protecting patients as about generating data for global databases. In hospital pharmacy practice, pharmacists need to be concerned that individual patients are protected from future exposure to drugs which have caused a problem (usually an allergy). Therefore the focus in training pharmacists should be on patient safety. This can be facilitated by creating alerts within the health care system as well as providing information which will help to protect the patient from future exposure, e.g. warning cards and medical alerts.

Preventing medication errors is a fundamental responsibility of pharmacists. The human elements which predispose to errors were outlined together with systems approaches to improve safety. It is important for health professionals to be able to report errors easily and without fear of punishment. Pharmacists should be a part of a multidisciplinary team to implement changes which will help to reduces future risks.

The power and the perils of the media when dealing with pharmacovigilance issues were demonstrated and led to animated discussion. Pharmacists' interactions with the media were also highlighted in a dedicated symposium later in the Congress.

The seminar demonstrated the interest and concerns of pharmacists from many different practice environments. Most importantly it demonstrated the links between individual patient care and patient safety at a global level.

Announcement:

A new online course in 'Drug Safety and Surveillance' is taking place between 9 January and 16 April 2012. Developed by the University of Bath, UK, the course aims to build expertise in regulatory aspects of drug safety, risk management, pharmacovigilance, pharmacoepidemiology and comparative effectiveness research. Limited spaces available, please register by 18 November 2011.

Further details are available at:
http://www.bath.ac.uk/pharmacy/postgraduate/drug_safety_surveillance
Email: DSS@bath.ac.uk or call +44 (0)1225 386773.