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

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No. 4, 2012

The WHO Pharmaceuticals Newsletter provides you with the latest information on the safety of medicines and legal actions taken by regulatory authorities across the world. It also provides signals from the Uppsala Monitoring Centre's SIGNAL document.

The feature articles in this issue give you information of new dosage recommendations for morphine and other opioid analgesics in children. And you will also find a summary of discussions and recommendations from the ninth meeting of the WHO Advisory Committee on Safety of Medicinal Products (ACSoMP).
## Regulatory Matters

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## Safety of medicines

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## Feature

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Calcitonin-containing medicines

**Intranasal formulation for osteoporosis treatment to be withdrawn; new restriction to indication for injectable use in Paget’s disease**

**Europe.** The European Medicines Agency’s Committee for Medicinal Products for Human Use (CHMP) recommended that calcitonin-containing medicines should only be used for short-term treatment, because of evidence that long-term use of these medicines is associated with an increased risk of cancer. Doctors should no longer prescribe calcitonin-containing medicines as nasal spray for the treatment of osteoporosis.

Taking into account the limited efficacy of calcitonin when used to treat post-menopausal osteoporosis to reduce the risk of vertebral fractures, the CHMP concluded that the benefits of calcitonin-containing medicines did not outweigh their risks in this indication. As the nasal spray is only used in osteoporosis, the CHMP recommended that this formulation be withdrawn.

For all other approved indications the CHMP considered that the benefit-risk balance remains positive, but recommended that calcitonin treatment should be given for the shortest possible time. For the treatment of patients with Paget’s disease, the CHMP also recommended limiting the use of calcitonin to a second-line indication in patients who do not respond to alternative treatments or for whom such treatments are not suitable. Treatment in this condition should normally be limited to 3 months; however, it may be extended to 6 months in exceptional circumstances, and intermittently repeated if it is considered that the potential benefits outweigh the risks.

Calcitonin will only be available as a solution for injection and infusion, and should only be used for:

- prevention of acute bone loss due to sudden immobilisation, with treatment recommended for two weeks with a maximum duration of four weeks;
- Paget’s disease in patients who do not respond to alternative treatments or for whom such treatments are not suitable, with treatment normally limited to three months;
- hypercalcaemia caused by cancer.

Treatment with calcitonin should be limited to the shortest possible time and using the minimum effective dose.

**Reference:**

**Candesartan**

**Fetal malformations**

**Australia.** The Therapeutic Goods Administration (TGA) reminded health-care professionals that candesartan and other angiotensin II receptor antagonists, as well as Angiotensin Converting Enzyme (ACE) inhibitors, are contraindicated in pregnancy. Exposure to these drugs in pregnancy can cause fetotoxicity. Patients who are pregnant or planning a pregnancy should be switched to an alternative antihypertensive agent.

The TGA advised that health-care professionals should review the use of angiotensin II receptor antagonists and ACE inhibitors in women of child-bearing age. These women should be advised of the risks to the fetus and counseled on the use of appropriate contraception to avoid inadvertent fetal exposure. Patients taking an angiotensin II receptor antagonist or ACE inhibitor should be advised to speak to their doctor if they may be pregnant, or planning a pregnancy. Women who are pregnant or planning a pregnancy should be switched to an alternative antihypertensive agent.

The TGA has received four reports of fetal abnormalities following candesartan use in pregnancy, including three reports in 2011. The TGA has also received reports of fetal abnormalities following the use of irbesartan, enalapril, lisinopril, perindopril and captopril during pregnancy.

Angiotensin II receptor antagonists and ACE inhibitors are classified as Australian pregnancy category D. Their use is contraindicated in pregnancy. Antihypertensives acting on the renin-angiotensin system have been associated with decreased renal function, oligohydramnios and retardation of skull ossification in the fetus. Their use in pregnancy has been associated with neonatal problems such as renal failure, hypotension and hypokalaemia. The risk of fetal abnormalities is considered greatest with second and third trimester exposure.

**Reference:**
Dabigatran etexilate

Positive benefit-risk balance confirmed. Modifications to product information for clearer guidance

Europe. The European Medicines Agency (EMA) recommended updating the product information for dabigatran etexilate (Pradax®), to give clearer guidance to doctors and patients on how to reduce and manage the risk of bleeding associated with the anticoagulant medicine.

On the basis of the available evidence, the CHMP concluded that the benefits of dabigatran etexilate continue to outweigh its risks and that it remains an important alternative to other blood-thinning agents. However, the advice to doctors and patients should be updated and strengthened to give clearer guidance on the best use of the medicine. This includes more specific guidance on when the drug must not be used as well as advice on managing patients and reversing the anticoagulant effect of the drug if bleeding occurs.

The EMA advised patients who are taking dabigatran etexilate or any other blood thinner to be aware that they are at an increased risk of bleeding. If they fall or injure themselves during treatment, especially if they hit their head, they should seek urgent medical attention.

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


Dalfampridine

Seizure risk for multiple sclerosis patients

USA. The U.S. Food and Drug Administration (US FDA) updated health-care professionals and the public about the risk of seizures in patients with multiple sclerosis (MS) who are starting dalfampridine (Ampyra®).

Dalfampridine was approved to improve walking in patients with MS. Seizures are a known side effect of the drug, and seizure risk increases with higher blood levels of the drug. Dalfampridine is eliminated from the body through the kidneys, and patients with kidney impairment may develop higher blood levels of the drug, thereby increasing their seizure risk.

The US FDA reminded health-care professionals that there are age-related decreases in renal function, and mild renal impairment is common after age 50, even when serum creatinine is normal. Renal function should be assessed by estimating creatinine clearance. Dalfampridine should not be used in patients with a history of seizures or who have moderate to severe renal impairment. A patient’s creatinine clearance (CrCl) should be known before initiating the treatment and monitored at least annually while the treatment continues, even when serum creatinine levels appear to be normal.

It is also advised to tell patients they should not take double or extra doses of dalfampridine if a dose is missed. Adverse effects, including seizures, are more frequent at higher doses.


Denosumab

Risk of severe symptomatic hypocalcemia, including fatal cases

Canada. Amgen Canada Inc., in collaboration with Health Canada, informed of new important safety information on severe symptomatic hypocalcemia associated with denosumab (XGEVA®) treatment.

Denosumab is indicated in patients with bone metastases from breast cancer, prostate cancer, non-small cell lung cancer, and other solid tumours for reducing the risk of developing skeletal-related events (SREs). The drug is not indicated in patients with multiple myeloma.

Post-marketing cases of severe symptomatic hypocalcemia have occurred at an estimated rate of 1 - 2%, including some cases which were fatal. Signs and symptoms of these cases included altered mental status, tetany, seizures and QTc prolongation, which were temporally associated with denosumab use, when serum calcium levels were decreased. Patients treated with denosumab should be informed of these symptoms and the need to seek immediate medical attention if they occur.

It is informed that the risk of severe symptomatic hypocalcemia among patients receiving denosumab may be minimized by the following:

- Correcting pre-existing hypocalcemia prior to initiating denosumab therapy.
Supplementing patients with calcium and vitamin D, unless hypercalcemia is present

Monitoring calcium levels as necessary while patients are receiving denosumab

Identifying risk factors for hypocalcemia in patients receiving denosumab. Patients with severe renal impairment (creatinine clearance < 30 mL/min) or receiving dialysis are at a greater risk of developing hypocalcemia in the absence of calcium supplementation.

If hypocalcemia occurs while receiving denosumab, additional short-term calcium supplementation may be necessary. If severe symptomatic hypocalcemia occurs, the benefit of continuing the treatment in these patients should be reassessed.

Reference:

Doripenem

Higher dosing may be needed in nosocomial pneumonia

Europe. The EMA gave new advice for the treatment of patients with nosocomial pneumonia with doripenem (Doribax®). A review of available data raises concerns that the currently approved dose of the drug of 500mg every 8 hours may not be sufficient to treat all patients with nosocomial pneumonia, including ventilator-associated pneumonia. Nosocomial pneumonia is caused by bacterial infection, and doripenem is one of a limited number of medicines available to treat this life-threatening disease.

For the treatment of patients with augmented renal clearance or with infections with non-fermenting gram-negative pathogens, the CHMP recommended that doctors double the dose to 1g every 8 hours. The Committee advised doctors that a longer treatment period (10-14 days) is required in patients with nosocomial pneumonia, including ventilator-associated pneumonia.

The Committee also advised doctors to exercise particular caution in patients for whom non-fermenting gram-negative pathogens such as Pseudomonas aeruginosa and Acinetobacter are suspected or confirmed as the cause of infection. In some of these patients, doctors should consider initiating concomitant treatment with an aminoglycoside antibiotic.

It is noted that, in addition to nosocomial pneumonia, doripenem is also used to treat complicated infections in the abdomen and the urinary tract. These indications were not affected by this review.

(See WHO Pharmaceuticals Newsletters No. 2, 2012 for higher mortality rate and a lower clinical cure rate observed during a comparative clinical trial in Canada.)

Reference:

Febuxostat

Stop treatment if signs or symptoms of serious hypersensitivity occur

UK. The Medicines and Healthcare products Regulatory Agency (MHRA) advised health-care professionals that febuxostat (Adenuric®) treatment should be stopped immediately if signs or symptoms of serious hypersensitivity reactions occur and must not be restarted in patients who have ever developed a hypersensitivity reaction to febuxostat, including Stevens-Johnson syndrome.

Febuxostat (Adenuric®) is a non-purine, xanthine oxidase inhibitor licensed for the treatment of chronic hyperuricaemia in adults, in whom urate deposition has already occurred (including a history, or presence of, tophus and/or gouty arthritis).

Since its launch in 2009 there have been rare but serious reports of hypersensitivity reactions to febuxostat, some associated with systemic symptoms. These have included rare reports of Stevens-Johnson syndrome and acute anaphylactic shock. In most cases, the reactions occurred during the first month of treatment. Some, but not all, of the patients experiencing hypersensitivity reactions to febuxostat were reported to have a prior history of hypersensitivity to allopurinol and/or renal disease.

It is also advised that patients should be informed of signs and symptoms of severe hypersensitivity or Stevens-Johnson syndrome. These include: infiltrated maculopapular eruption; generalised or exfoliative rashes; skin lesions; facial oedema, fever, haematologic abnormalities such as thrombocytopenia, a single or multiple organ involvement (liver and kidney including tubulointerstitial nephritis), progressive skin rashes associated with blisters or mucosal lesions and eye irritation.

Reference:

Tolperisone

Benefit-risk profile for oral tolperisone considered positive only for adults with post-
stroke spasticity and negative for injectable tolperisone

Europe. The EMA recommended restricting the use of tolperisone, a muscle relaxant authorised to treat a variety of different conditions, including spasticity due to neurological disorders and muscle spasms associated with diseases of the spine and large joints in several European Union countries since the 1960s.

The EMA recommended that doctors should stop prescribing tolperisone for any indication other than post-stroke spasticity in adults. They should also no longer use injectable tolperisone.

It is advised that patients currently using tolperisone for any other indication or using injectable tolperisone should speak to their doctor at their next routine appointment so they can switch to an appropriate alternative treatment. Patients should be made aware of the possibility of developing hypersensitivity reactions during treatment with tolperisone. They should stop treatment with tolperisone and speak to their doctor if they experience symptoms such as flushing, rash, severe itching of the skin (with raised lumps), wheezing, difficulty breathing, difficulty in swallowing, fast heartbeat, low blood pressure or a fast decrease in blood pressure.

The above advice follow the review by the CHMP that was initiated by Germany following concerns over several hypersensitivity reactions reported post-marketing and insufficiently demonstrated efficacy in some indications.

Reference:

Trimetazidine-containing medicines

Restricted use in patients with stable angina pectoris and deletion of existing indications for treatment of vertigo, tinnitus and vision disturbance

Europe. The EMA recommended restricting the use of trimetazidine-containing medicines in the treatment of patients with angina pectoris to second-line, add-on therapy. For all other indications, the CHMP concluded that the benefits of these medicines were not sufficiently demonstrated and did not outweigh the risks. The CHMP therefore recommended their deletion from the marketing authorisation. It is advised that there is no need for an urgent change in treatment, but doctors should review their patients’ treatment at their next routine appointment.

It is advised that;

- Doctors should no longer prescribe trimetazidine for the treatment of patients with tinnitus, vertigo or disturbances in vision. Patients who are taking trimetazidine in these indications should discuss alternatives with their doctor.
- Doctors can continue to prescribe trimetazidine for the treatment of angina pectoris, but only as an add-on therapy for the symptomatic treatment of patients with stable angina pectoris who are inadequately controlled by or intolerant to first-line anti-anginal therapies.

The review was initiated by France, mainly because of concerns that the efficacy of trimetazidine was not sufficiently demonstrated. It also looked at reports regarding the occurrence of movement disorders such as Parkinsonian symptoms, restless leg syndrome, tremors and gait instability associated with the medicine. Although patients usually recovered fully within four months after treatment with trimetazidine was discontinued, the Committee recommended new contraindications and warnings to reduce and manage the possible risk of movement disorders associated with the use of this medicine.

Doctors are advised not to prescribe the medicine to patients with Parkinson’s disease, Parkinsonian symptoms, tremors, restless-leg syndrome or other related movement disorders, nor to patients with severe renal impairment. Doctors should exercise caution when prescribing trimetazidine to patients with moderate renal impairment and to elderly patients, and consider dose reduction in these patients.

It is also advised that trimetazidine should be discontinued permanently in patients who develop movement disorders such as Parkinsonian symptoms. If Parkinsonian symptoms persist for more than four months after discontinuation, a neurologist’s opinion should be sought.

Reference:
Hepatitis B Immune Globulin (Human) Injection

Theoretical risk of thrombotic events with intravenous administration

Canada. Cangene Corporation, in cooperation with Health Canada, informed of planned changes to the Canadian product monograph for Hepatitis B Immune Globulin (Human) (HepaGam B®), including pertinent precautions regarding thrombotic events.

There is a theoretical risk for the arterial and venous thrombosis at the intravenous doses of HepaGam B® for the liver transplantation indication. Such a risk may exist because an in-house analysis detected measurable levels of procoagulant (factor XIa) activity in HepaGam B®. The significance of these levels is being evaluated. Changes to the manufacturing process for HepaGam B® are planned to minimize the occurrence of procoagulant activity.

It is advised that patients should be informed of signs and symptoms of thrombotic events and that caution should be used when administering immune globulins, including HepaGam B®, to patients with risk factors for thrombotic events.

Patients at risk include those with a history of atherosclerosis, cardiovascular risk factors, impaired cardiac output, coagulation disorders, prolonged periods of immobilization, advanced age and/or known/suspected hypertension from any cause, including dehydration.

Physicians should inform patients of the symptoms of a thrombotic event, including shortness of breath, pain and swelling of a limb, focal neurological deficits, chest pain, and other manifestations of thrombotic and embolic events. Patients should also be informed what to do if these symptoms occur.

Reference:

Immune Globulin Intravenous (Human)

Association of haemolysis following administration and related labelling update

Canada. CSL Behring Canada, Inc., in collaboration with Health Canada informed of a recent labelling update regarding the risk of haemolysis following Immune Globulin Intravenous (Human) (Privigen®) administration.

Delayed haemolytic anaemia and acute haemolysis have been reported following therapy with Immune Globulin Intravenous (Human). Isolated cases of haemolysis-related renal dysfunction/failure or disseminated intravascular coagulation have occurred. Increased vigilance is recommended in patients with the following risk factors for developing a haemolytic reaction:

- High doses (whether given as a single administration or divided doses over several days),
- Non-O blood group, and
- Possibly, an underlying inflammatory state.

Immune Globulin Intravenous (Human) or IGIV recipients should be closely monitored for clinical signs and symptoms of haemolysis. If signs and/or symptoms of haemolysis are present after IGIV infusion, appropriate confirmatory laboratory testing should be performed. If transfusion is indicated for patients who develop haemolytic anaemia after receiving IGIV, cross-matching should be performed.

(See WHO Pharmaceuticals Newsletter No. 6, 2009 and No.1, 2010 for risk of haemolytic reactions with intravenous immune globulin in Canada)

Reference:

Oral tacrolimus

Prescribe and dispense by brand name only

UK. The MHRA recommended that oral tacrolimus products should be prescribed and dispensed by brand name only to ensure maintenance of therapeutic response when a patient is stabilised on a particular brand, and to minimise the risk of inadvertent switching between products from different suppliers. If a prescriber considers that switching a patient to a different brand of oral tacrolimus would be of benefit, the change requires careful supervision and therapeutic monitoring by an appropriate specialist.

Since 2008, the MHRA has been aware of reports of unintended switching between different pharmaceutical forms of oral tacrolimus products in patients who have been treated with tacrolimus for the prevention of organ transplant rejection. Graft rejection reactions and tacrolimus toxicity have resulted from a small number of these unintended switches between products.

As there are a growing number of tacrolimus products available on the UK market, the Commission on Human Medicines (CHM) has now advised that the risk of inadvertent switching between the different products may increase. Therefore, as a
precautionary measure, the CHM has updated its advice on the safer use of oral tacrolimus products and recommends that all oral tacrolimus products should be prescribed and dispensed by brand name only. This supersedes previous advice regarding the prescribing, dispensing and interchangeability of different tacrolimus products (see Drug Safety Update January 2009, February 2010, and May 2010).

The MHRA also advised that pharmacists should always dispense the exact brand prescribed. They should contact the prescriber if the prescription is not clear to ensure the appropriate medicine is dispensed and that patients should be advised to take careful note of the brand name of their usual tacrolimus medicine and should check with their doctor or pharmacist if they receive a different brand or if they have any other questions about the prescription, eg about the dose.

(See WHO Pharmaceuticals Newsletters No. 3, 2010 for measures to reduce risk of medication errors in UK.)

**Reference:**
Bisphosphonates, corticosteroids, angiogenesis inhibitors and denosumab

Osteonecrosis of the Jaw (ONJ)

New Zealand. The Medicines and Medical Devices Safety Authority (Medsafe) advised health-care professionals to recommend oral hygiene measures and closely monitor patients who are at risk of experiencing Osteonecrosis of the Jaw (ONJ), which is associated with a number of medicines and is a potentially debilitating condition that is difficult to treat.

ONJ is characterised by the presence of necrotic, exposed bone in the jaw. The jaws are particularly sensitive to osteonecrosis due to high bone turnover resulting from daily activity and the presence of teeth. Patients usually experience pain, possible secondary swelling, painful lesions, tooth mobility, ulceration and various dysesthesias. However, patients can also be asymptomatic.

Medicines associated with the development of osteonecrosis include bisphosphonates (both oral and intravenous), corticosteroids, angiogenesis inhibitors such as bevacizumab (Avastin®) and sunitinib (Sutent®) and denosumab (Prolia®).

Additional factors that may have an additive impact on the risk of ONJ are invasive dental procedures, radiotherapy, renal insufficiency, alcohol use, smoking, obesity, increasing age, anaemia, diabetes, rheumatoid arthritis and vitamin D deficiency.

To date, the Centre for Adverse Reactions Monitoring (CARM) has received a total of 28 reports of ONJ that they considered to be related to the medicine. Alendronic acid was suspected in 13 cases, pamidronic acid in 11 cases and zoledronic acid in seven cases (some cases involved more than one suspect medicine).

(See WHO Pharmaceuticals Newsletters No. 1, 2011 for safety measures against osteonecrosis and osteomyelitis of jaw in Japan and UK, and No. 1, 2010, No. 1, 2008, No.5, 2006 and No.6, 2004 for a review on the risk of osteonecrosis of the jaw in Europe, reports of osteonecrosis of the jaw in Australia, and reports of osteonecrosis of the jaw in the USA, respectively.)

Reference:

Butterbur

Liver toxicity

New Zealand. Medsafe advised health-care professionals that reports of liver toxicity associated with Butterbur have been received overseas. Medsafe encouraged health-care professionals to ask patients about their use of complementary and alternative medicines and to report any suspected adverse reactions to the CARM.

Butterbur, Petasites hybridus, is a member of the ragweed family that is native to the northern United States and Canada. Butterbur is traditionally used for the treatment of hay fever, migraine and asthma. Butterbur contains unsaturated pyrrolizidine alkaloids that are known to be hepatotoxic in humans and in preclinical studies have been shown to be carcinogenic and mutagenic. Pyrrolizidine alkaloids may be present in low concentrations in all parts of the plant. It is possible to reduce the unsaturated pyrrolizidine alkaloids to low levels during the manufacturing process. However, cases of liver toxicity have been reported with extracts of butterbur where the pyrrolizidine alkaloids had been removed and only small amounts remained.

A search of the World Health Organization’s pharmacovigilance database, VigiBase, revealed reports of adverse reactions involving the liver in association with products containing Petasites hybridus. VigiBase reports include nausea, anorexia and pruritus to hepatic enzymes increased, hepatic necrosis, hepatocellular damage, jaundice, hepatitis and hepatic failure. In the literature, 40 cases of liver toxicity in association with butterbur have been reported. Cases included nine of acute hepatitis and two of liver failure requiring transplantation.

Reference:

Caffeine citrate

Care needs when using two products of different strengths

UK. The MHRA announced that two caffeine citrate products for the treatment of primary apnoea of premature newborns are available: a generic product which contains 10 mg/mL caffeine citrate and a new product called Peyona®, which contains 20 mg/mL of caffeine citrate. The agency advised health-care professionals to take careful note of which product is being used, to avoid dosing errors.

Other advices for health-care professionals are:
• Caffeine citrate is for use in neonatal Intensive Care Units only and treatment must be initiated under the
supervision of a physician experienced in neonatal intensive care

- Health-care professionals should also pay special attention to the contraindications, warnings and precautions for use when prescribing and administering caffeine citrate products.
- During treatment with any caffeine citrate product, measurement of baseline caffeine levels, monitoring of plasma caffeine concentrations, as well as dose adjustments during treatment, are advisable, particularly in cases of insufficient response or toxic effects, or in infants who are at an increased risk of elevated plasma concentrations (eg, very premature infants or those who have hepatic or renal impairment).
- It is also advisable to measure baseline caffeine levels in infants whose mothers have ingested large quantities of caffeine prior to delivery or infants who previously have been treated with theophylline.

**Reference:**

### Non-steroidal anti-inflammatory drugs

#### Risk of Severe Cutaneous Adverse Reaction (SCAR)

**New Zealand.** Medsafe reported that Non-steroidal anti-inflammatory drugs (NSAIDs) can cause severe cutaneous adverse reactions (SCARs) in rare cases. SCARs include bullous eruptions, erythema multiforme, epidermal necrolysis, toxic epidermal necrolysis and Stevens Johnson syndrome.

The CARM received a number of reports of SCARs associated with NSAIDs. SCARs may cause permanent sequelae such as disfigurement, blindness and death. Importantly, these reactions may occur without warning. The overall risk of SCARs associated with the use of NSAIDs is extremely low. The highest reported incidence is with celecoxib at six cases per 1 million person-years. In New Zealand, the NSAIDs most commonly reported to cause SCARs are piroxicam, naproxen, diclofenac, celecoxib and ibuprofen.

SCARs are idiosyncratic and independent of dose or duration of use. People who appear most at risk are older patients, women and those early in the course of therapy. The onset of these reactions generally occurs within the first month of treatment.

It is advised that prescribers should advise patients of the signs and symptoms of SCARs. Patients should be advised to consult their doctor at the first appearance of a skin rash, new onset fever without explanation, mucosal lesions or any sign of hypersensitivity. If a SCAR occurs, NSAID treatment should be discontinued immediately.

**Reference:**

### Peanut Oil

#### Risk of allergic reactions

**New Zealand.** Medsafe advised health-care professionals to consider the potential for allergic reactions to occur when prescribing or dispensing medicines to patients with a known peanut allergy. Medsafe is working with the sponsors of medicines containing peanut oil to improve labelling.

The CARM has recently received a report of an allergic skin reaction in a patient after receiving her first dose of a medicine. The patient had a known peanut allergy but only discovered later that the medicine contained peanut oil.

The peanut oil used in medicines is highly refined and the majority, if not all, of the peanut protein is removed during manufacturing. However, as life-threatening allergic reactions can occur with minimal exposure to peanut, caution is recommended with the use of medicines containing peanut oil in patients with a known peanut allergy.

**Reference:**

### Serotonergic medicines

#### Risk of Reversible Cerebral Vasoconstriction Syndrome (RCVS)

**New Zealand.** A recent Medsafe review confirmed that cases of Reversible Cerebral Vasoconstriction Syndrome (RCVS) have been reported in association with the use of serotonergic medicines. Cases of RCVS have been reported with duloxetine, sertraline, citalopram, paroxetine, fluoxetine and sumatriptan. However, this data is currently inadequate to confirm a causal association.

RCVS is a unifying term used to describe a diverse range of conditions characterised by recurrent thunderclap headaches and reversible segmental cerebral arterial vasoconstriction on angiogram. Conditions include Call-Fleming syndrome, benign angiopathy of the CNS, postpartum angiopathy or idiopathic thunderclap headache. RCVS should be considered in the differential diagnosis of
thunderclap headaches when other causes have been excluded.

RCVS is thought to be under-reported for many reasons including lack of awareness of the condition and difficulties in confirming the diagnosis. The current data on RCVS comes primarily from case series conducted in Taiwan, France and the US. The case series included 262 patients who experienced RCVS.

Medsafe has added prescribers to report all cases of recurrent thunderclap headaches or suspected RCVS associated with serotonin to the CARM. Prescribers should report cases even if an angiogram has not been performed.


Statins and ciclosporin

Increased risk of statin-related adverse events including myopathy

New Zealand. Medsafe advised that patients taking a statin with ciclosporin may be at increased risk of statin-related adverse events. In patients currently taking ciclosporin, who also required lipid-lowering therapy, statins should be used with care. Prescribers should use the lowest possible dose and monitor for adverse reactions and the effectiveness of treatment.

Dyslipidaemia is common in patients who have undergone solid organ transplantation. Dyslipidaemia is estimated to occur in up to 80% of renal, pancreas, and heart transplant recipients and up to 45% of liver transplant patients. In addition, immunosuppressant therapy, including corticosteroids and ciclosporin, have all been associated with dyslipidaemia. For these reasons, it is common for transplant patients to require statin therapy.

Pharmacokinetic studies confirm that ciclosporin interacts with all statins to increase the plasma levels of the statin. Myopathies are the most severe adverse reaction to statin therapy. The risk of myopathy increases with increasing plasma levels of statins.

Other risk factors for statin-induced myopathy include female gender, a decline in renal or hepatic function, low body mass index, hypothyroidism and a personal or family history of symptoms associated with rhabdomyolysis.


Tacrolimus ointment

A possible risk of malignancies including lymphomas and skin cancers

UK. The MHRA reminded health-care professionals that tacrolimus ointment (Protopic®) should not be prescribed to patients younger than 2 years, and that the use of tacrolimus ointment in children aged 2 – 16 years is restricted to the lower strength 0.03% ointment only. In addition, tacrolimus ointment should not be applied to lesions that are considered to be potentially malignant or pre-malignant, or used in patients with congenital or acquired immunodeficiencies, or in patients on therapy that causes immunosuppression.

Tacrolimus ointment is used to treat moderate to severe atopic dermatitis flares, and to maintain flare-free intervals, in adults and adolescents age 16 years and older, who do not respond to, or are intolerant of, conventional therapies such as topical corticosteroids.

Protopic is available in two strengths containing tacrolimus 0.03% and 0.1%, respectively. The lower strength ointment can be used to treat moderate to severe atopic dermatitis in children of 2 years and above, as well as adults and adolescents. The higher strength ointment is licensed only for use in patients aged 16 years and older.

The MHRA reminded health-care professionals that tacrolimus may be associated with a possible risk of malignancy. Benign as well as malignant neoplasms including Epstein-Barr virus-associated lymphoproliferative disorders and skin malignancies have been reported in association with oral (systemic) tacrolimus treatment.

Cases of malignancies, including lymphomas and skin cancers have also been reported in patients using topically applied tacrolimus since it was licensed in 1999.


Zolpidem

Continued reporting of abnormal sleep-related events and amnesia

Australia. The TGA announced that the agency continues to receive reports of potentially dangerous, complex sleep-related behaviors, amnesia and hallucinations associated with zolpidem use. The TGA advised that, when considering the use of zolpidem in the management of insomnia, prescribers should advise patients of the contraindications and precautions listed in the
Product Information (PI), and of the spectrum of adverse effects associated with zolpidem use. The TGA also encouraged health-care professionals to report cases to the TGA, including suspected cases.

A study of reports received by the TGA between 2001 and 2008 concluded that there was 'an association between zolpidem exposure and parasomnias, amnesia and hallucination both before and after the cluster of media publicity beginning in early 2007'. Despite the publicity, reporting of these adverse events has persisted at high levels.

(See WHO Pharmaceuticals Newsletter No.1, 2012 for association with complex sleep behaviours in Canada and No. 2, 2008 for boxed warning added about sleep disorders in Australia.)

Reference:
Medicines Safety Update Vol 3, No. 3, June 2012
A signal is defined by WHO as reported information on a possible causal relationship between an adverse event and a drug, the relationship being unknown or incompletely documented previously. Usually more than a single report is required to generate a signal, depending upon the seriousness of the event and the quality of the information. A signal is a hypothesis together with data and arguments and it is important to note that a signal is not only uncertain but also preliminary in nature.

The signals in this Newsletter are based on information derived from Individual Case Safety Reports (ICSRs) available in the WHO Global ICSR database, VigiBase™. The database contains over 7 million reports of suspected adverse drug reactions, submitted by National Pharmacovigilance Centres participating in the WHO Programme for International Drug Monitoring. VigiBase is, on behalf of the WHO, maintained by the Uppsala Monitoring Centre (UMC) and periodic analysis of VigiBase data is performed in accordance with UMC’s current routine signal detection process.

More information regarding the ICSRs, their limitations and proper use, is provided in the UMC Caveat document available at the end of SIGNAL (page 22). For information on the UMC Measures of Disproportionate Reporting please refer to WHO Pharmaceuticals Newsletter Issue No. 1 2012.

UMC, a WHO Collaborating Centre, is an independent foundation and a centre for international service and scientific research within the field of pharmacovigilance. UMC’s vision is to improve worldwide patient safety and welfare by reducing the risk of medicines. For more information, visit www.who-umc.org. To leave a comment regarding the signals in this Newsletter, please contact: the Uppsala Monitoring Centre, Box 1051, SE-751 40 Uppsala, Sweden. E-mail: info@who-umc.org.

Dronedarone, hyperthyroidism and decreased Thyroid Stimulating Hormone
Ruth Savage, New Zealand

Summary
There are 23 reports of hyperthyroidism or decreased thyroid stimulating hormone associated with dronedarone in VigiBase™. Dronedarone is a benzofuran derivate that has been developed to overcome the iodine-associated adverse effects of amiodarone, to which it is otherwise chemically related. If abnormalities in thyroid function do occur with dronedarone, it is likely that they will be similar to the inherent adverse thyroid effects attributed to amiodarone but not to those attributed to its iodine content. In some of the reports found in VigiBase it is possible that patients who developed hyperthyroidism on amiodarone were still experiencing fluctuating disease while taking dronedarone due to the long half-life of amiodarone. There are however reports where there is no history of exposure to amiodarone or where substantial time has passed since the amiodarone treatment ended. The increase in number of reports of hyperthyroidism and decreased thyroid stimulating hormone associated with dronedarone suggests that there may be a relationship where dronedarone either causes the adverse reaction or exacerbates the reaction caused by amiodarone.

Introduction
Routine screening of suspected adverse drug reactions reported to the WHO Global Individual Case Safety Report (ICSR) database, VigiBase™, has identified a recent increase in numbers of reports of hyperthyroidism and decreased thyroid stimulating hormone (TSH) associated with dronedarone use.

Dronedarone is a benzofuran derivate that has been developed to overcome the iodine-associated extra cardiac adverse effects of amiodarone. It has similar clinical indications and a chemically related structure to amiodarone but lacks the iodine component.1 Dronedarone possesses a methane sulphonyl group that decreases its lipophilicity resulting in a shorter half-life and less tissue accumulation than amiodarone. Dronedarone has an elimination half-life of 24 hours compared with up to 100 days for amiodarone. It undergoes considerable hepatic first pass metabolism involving CYP isoenzymes 3A4 and 2D6. It is also an inhibitor of CYP 3A4 and 2D6 and P-glycoprotein transport.

Adverse effects of amiodarone on the thyroid gland
Adverse effects of amiodarone include various thyroid disorders, some attributed to its iodine content and others considered inherent effects of amiodarone. It is useful therefore, before
considering the dronedarone reports, to review the mechanisms whereby amiodarone can adversely affect the thyroid gland. The underlying thyroid status of individuals and their environment predispose them to specific amiodarone-induced thyroid disorders.\(^2\)

The effects on the thyroid due to the iodine content of amiodarone are hypothyroidism in patients with autoimmune thyroid disease and hyperthyroidism in patients with autonomous function in a nodular goitre.

**Inherent effects of amiodarone on the thyroid gland**

Thyroid dysfunction may occur due to inhibition of 5'-monodeiodination leading to decreased circulating triiodothyronine (T3) and increased reverse T3, thyroxine (T4) and TSH. These effects are common and tend to occur in the first few months of treatment after which serum T4 and TSH levels tend to return to normal. Amiodarone can exert a direct toxic effect on follicular thyrocytes leading initially to hyperthyroidism. There are two forms of amiodarone-induced thyrotoxicosis (AIT), type I AIT and type II AIT. Type I occurs predominantly in areas of iodine deficiency and a high incidence of goitre whereas type II tends to occur where iodine is sufficient and there is a low incidence of toxic multinodular goitre. Type II AIT is due to a direct cytotoxic effect on thyroid follicles leading to an inflammatory reaction and follicular disruption allowing leakage of large amounts of thyroid hormones into the circulation.

If abnormalities in thyroid function do occur with dronedarone it is likely that they will be similar to the adverse thyroid effects attributed to amiodarone but only to those considered inherent effects rather than those attributed to its iodine content. Consideration was therefore given to whether the reports in Vigibase of hyperthyroidism and decreased TSH with dronedarone were in keeping with this hypothesis.

**Reports in Vigibase**

In Vigibase there are 20 reports of hyperthyroidism and six of decreased TSH attributed to dronedarone. Three reports contained both ADR terms and therefore 23 reports were assessed. The reports originated from ten countries: Austria, Canada, Germany, Denmark, Spain, Ireland, Lithuania, Norway, Great Britain and the USA.

**Patient Characteristics**

Thirteen patients were males, six were females and gender was not specified in four reports. Age was recorded for 18 patients and ranged from 30 to 76 years, mean 61.1 years, median 61.5 years.

Indications for dronedarone use, recorded for 18 patients, were atrial fibrillation, atrial flutter and cardiac arrhythmia. Four patients had developed hyperthyroidism while taking amiodarone prior to starting dronedarone. Two other patients also had a history of hyperthyroidism although this was not clearly attributed to amiodarone. One patient had a diencephalic endocrinopathy.

**Characteristics of dronedarone use**

Daily dose was recorded for 15 patients and was 800 mg (13) or 400 mg (2). Duration of dronedarone use to onset of hyperthyroidism was recorded in 10 reports and was 5 months or less in nine reports and 14 months in the tenth. In reports for decreased TSH but not hyperthyroidism, duration of dronedarone use to onset was not recorded.

**Report Assessment**

Causality assessment for the reports in these combinations is complicated by the fact that many patients change from amiodarone to dronedarone because of amiodarone adverse effects and these include hyperthyroidism. Some reports indicate that the patient did develop hyperthyroidism on amiodarone prior to starting dronedarone. Other patients were recorded as having pre-existing hyperthyroidism but amiodarone was not described as the cause.

Dronedarone was the sole suspect medicine in 16 reports. Amiodarone was recorded as co-suspect in six and described as co-prescribed in three. However, in reports that included dates, amiodarone was always discontinued before dronedarone was commenced. Thiamazole and metoprolol were co-suspects in one report of decreased TSH. The patient had pre-existing hyperthyroidism and it is unlikely that these medicines caused the abnormality. No other suspect medicines were recorded in the reports.

The reports were divided according to causality assessment and completeness of information especially regarding past history and history of amiodarone use or non-use. Table 1 indicates those reports that were considered by the reviewer to be at least possibly related to dronedarone use and that contained either past history and/or narrative.

In the first report in Table 1, the patient recovered when dronedarone was discontinued and treatment for hyperthyroidism commenced. Although she had a diencephalic endocrinopathy, thyroid and adrenal function were normal on starting dronedarone and there was no history of exposure to amiodarone or hyperthyroidism. She developed severe symptomatic hyperthyroidism with weight loss, tremor, sweating and restlessness. Patients 2 and 3 in Table 1 had no history of hyperthyroidism. Both had been exposed to amiodarone but had changed to...
dronedarone four and five months before hyperthyroidism developed. Patient 4 had developed hyperthyroidism on amiodarone. However, there was a marked increase in thyroid hormones five months after dronedarone was started, seven months after amiodarone was discontinued suggesting a de novo effect of dronedarone or an additive or exacerbating effect on amiodarone-induced hyperthyroidism. Patient 5 had developed an abnormal TSH level on amiodarone although whether this was increased or decreased was not recorded. This patient recovered from extra systoles and thyrotoxicosis when dronedarone was discontinued.

Table 2 contains reports that can be assessed as “possible” based on the information provided but should be interpreted with caution as they lack past history and/or narrative so that previous amiodarone use may not have been documented. The remaining reports, not included in the tables, contained insufficient information for causality assessment or they contained information that suggested that the reactions were unlikely to be related to dronedarone. The latter reports included narrative information indicating that the patients most likely had amiodarone-related hyperthyroidism.

**Literature and Labelling**

In the ATHENA (A placebo-controlled, double-blind, parallel-arm Trial to assess the efficacy of dronedarone 400 mg bid for the prevention of cardiovascular Hospitalization or death from any cause in patients with Atrial fibrillation/atrial flutter) study of 4628 subjects randomised to dronedarone 800 mg daily or placebo with a duration of 21 +/- 5 months, the rates of thyroid adverse events were not different between the two groups. In the EURIDIS, ADONIS twin studies of 612 and 625 subjects taking dronedarone 800 mg daily or placebo over one year, the incidence of hyperthyroidism was 8.4% in subjects taking dronedarone and 14.1% in those assigned to placebo. In these twin studies, hyperthyroidism was defined as a free T3 level or free T4 level above the normal range or a thyrotropin (TSH) level below the normal range. The severity of these changes and whether they were clinically important was not described.  

The DIONYSOS (randomized double blind trial to evaluate the efficacy and safety of dronedarone versus amiodarone for at least 6 months for the maintenance of sinus rhythm in patients with atrial fibrillation) study, including 504 subjects, compared the efficacy and safety of dronedarone (400 mg twice daily) versus amiodarone (600 mg daily for 28 days, then 200 mg daily thereafter) over 6 months. The incidence of specific adverse effects (“thyroid, hepatic, pulmonary, neurological, skin, eye or gastrointestinal specific events or adverse event”) was 20% lower in the dronedarone group compared to the amiodarone group (p=0.129), including significantly fewer thyroid events in the dronedarone group.  

**Discussion and Conclusion**

The most likely diagnosis for the patients in the reports who developed hyperthyroidism on amiodarone is Type II AIT. This may also be true for those who first developed hyperthyroidism on dronedarone. Supporting evidence comes from reports with laboratory results showing an elevated T4 and markedly suppressed TSH. The TSH was increased in one patient with hyperthyroidism (report 5 in Table 2) suggesting an inhibition of monodeiodination as the mechanism rather than AIT in this one report. Type II AIT is slow to remit after amiodarone is withdrawn and may in fact be exacerbated by withdrawal as the protection against the arrhythmias of hyperthyroidism is removed.

It is therefore possible that patients who had developed hyperthyroidism on amiodarone were still experiencing fluctuating disease while taking dronedarone. Several patients developed a recurrence of atrial fibrillation. This may have been due to dronedarone-induced hyperthyroidism but recurrence of previous thyroid-related atrial arrhythmias may have occurred if dronedarone was less effective than amiodarone at controlling these.

The well-documented reports in Table 1 are the key reports in discussing this issue. Patient 1 had a detailed past history with no mention of hyperthyroidism or exposure to amiodarone. Although she had a history of diencephalic endocrinopathy and adrenal hyperplasia she had normal adrenal function and was euthyroid prior to starting dronedarone. She also recovered on dechallenge together with thiamazole treatment. The differential diagnoses considered by her physician were Basedow’s (Graves’) disease and dronedarone-induced hyperthyroidism. Patients 2 and 3 had been exposed to amiodarone but there was no mention of previous hyperthyroidism. Also the hyperthyroidism with dronedarone occurred several months after amiodarone was stopped and dronedarone commenced. The fourth case report in Table 1 concerns a patient with a history of amiodarone-induced hyperthyroidism who developed a marked increase in thyroid hormones detected five months after dronedarone was commenced. Amiodarone-induced hyperthyroidism can relapse after amiodarone has been discontinued because of the long half-life of this medicine. However, this patient had not taken amiodarone for seven months. He may have...
experienced a relapse but a de novo effect of dronedarone or an exacerbating or additional effect of dronedarone are alternative explanations. The reports in Table 2 do not contain past history or narrative, but the duration of dronedarone use, and therefore length of time since any amiodarone use, of 8 months and 14 months for two patients increases the likelihood of a dronedarone adverse effect.

The reports provide some evidence for an adverse effect of dronedarone on the thyroid gland causing hyperthyroidism. It may have a destructive effect on the thyroid follicles similar to AIT II, an inherent effect of amiodarone or, in some cases, may exacerbate such effects after they have occurred with amiodarone.

Table 1. Dronedarone and hyperthyroidism and/or TSH decreased. Causality at least possible as assessed by reviewer. Past history and/or narrative available in the reports.

<table>
<thead>
<tr>
<th>Case</th>
<th>Gender / Age</th>
<th>Relevant past History</th>
<th>ADR Terms</th>
<th>Dronedarone Daily Dose and duration to ADR onset</th>
<th>Amiodarone use</th>
<th>Indication</th>
<th>Suspect Drugs (as stated by reporter)</th>
<th>Dechallenge and Outcome (at time of reporting)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>F/58</td>
<td>Diencephalic Endocrinopathy Hyperplasia adrenal (TSH, T4, T3 normal day before started dronedarone)</td>
<td>Anti-thyroid antibodies (including thyroglobulin) T4 increased T3 increased TSH decreased Hyperthyroidism (massive)</td>
<td>400mg/37 days</td>
<td>-</td>
<td>Atrial fibrillation.</td>
<td>Dronedarone</td>
<td>Dronedarone withdrawn Recovering with treatment (thiamazole)</td>
</tr>
<tr>
<td>2</td>
<td>M/74</td>
<td>Thyrotoxicosis (TSH decreased Free T4 increased) Rash</td>
<td>-/5 months</td>
<td>Amiodarone stopped two weeks before dronedarone started</td>
<td>Cardiac Arrhythmia</td>
<td>Dronedarone</td>
<td>Dronedarone withdrawn Unknown outcome</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>M/63</td>
<td>Thyroid function normal on amiodarone</td>
<td>Hyperthyroidism (no clinical manifestations)</td>
<td>800 mg/4 months</td>
<td>Amiodarone taken for seven months until dronedarone started</td>
<td>Atrial fibrillation</td>
<td>Dronedarone Amiodarone</td>
<td>Dronedarone continued Not recovered</td>
</tr>
<tr>
<td>4</td>
<td>M/32</td>
<td>Hyperthyroidism, amiodarone-induced</td>
<td>Hyperthyroidism. (Marked increase in thyroid hormones since dronedarone started - T4 increased, TSH decreased)</td>
<td>-/5 months</td>
<td>Amiodarone stopped due to hyperthyroidism 2 months before dronedarone started</td>
<td>-</td>
<td>Dronedarone Amiodarone</td>
<td>Dronedarone continued Not recovered</td>
</tr>
</tbody>
</table>
Table 2. Dronedarone and hyperthyroidism and/or TSH decreased. Causality possible as assessed by reviewer. Past history and/or narrative absent or clearly incomplete in the reports.

<table>
<thead>
<tr>
<th>Case</th>
<th>Gender/Age</th>
<th>ADR Terms</th>
<th>Dronedarone Daily Dose and duration to ADR onset</th>
<th>Indication</th>
<th>Suspect Drugs (as stated by reporter)</th>
<th>Dechallenge and Outcome at time of reporting</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>F/71</td>
<td>Hyperthyroidism</td>
<td>800 mg/4 months</td>
<td>Atrial fibrillation</td>
<td>Dronedarone continued</td>
<td>Dronedarone withdrawn</td>
</tr>
<tr>
<td>2</td>
<td>F/70</td>
<td>Hyperthyroidism, Atrial fibrillation</td>
<td>800 mg/14 months</td>
<td>Atrial fibrillation</td>
<td>Dronedarone continued</td>
<td>Dronedarone withdrawn</td>
</tr>
<tr>
<td>3</td>
<td>F/76</td>
<td>Hyperthyroidism, Atrial fibrillation</td>
<td>800 mg/3 months</td>
<td>Atrial fibrillation</td>
<td>Dronedarone continued</td>
<td>Dronedarone withdrawn</td>
</tr>
<tr>
<td>4</td>
<td>M/75</td>
<td>TSH decreased, T4 abnormal, Glomerular filtration rate decreased, Renal failure, Tachyarrhythmia</td>
<td>-/5 months duration of use, but time to ADR onset unknown</td>
<td>Dronedarone</td>
<td>Dronedarone withdrawn</td>
<td>Dronedarone withdrawn</td>
</tr>
<tr>
<td>5</td>
<td>M/59</td>
<td>Hyperthyroidism, Alanine amino-transf erase increased</td>
<td>800 mg/4-5 months</td>
<td>Atrial fibrillation</td>
<td>Dronedarone</td>
<td>Dronedarone withdrawn and thiamizole started</td>
</tr>
<tr>
<td>6</td>
<td>-/-</td>
<td>Hyperthyroidism</td>
<td>-/Approximately 8 months after therapy switch from amiodarone to dronedarone.</td>
<td>Amiodarone</td>
<td>Dronedarone</td>
<td>Dronedarone continued</td>
</tr>
</tbody>
</table>

References
Response from MAH, Sanofi, regarding a signal between Dronedarone Hyperthyroidism and decreased Thyroid Stimulating Hormone

Dronedarone is similar to amiodarone in its molecular structure with an important difference consisting in the absence of iodine in the former. Amiodarone is known to be able to induce thyroid disorders, both hypo and hyperthyroidism, mainly due to the high supply of iodine. However amiodarone may also induce iodine-independent thyroid disorders, involving an immune pathogenetic mechanism, such as amiodarone-induced thyreotoxicosis type II (AIT II). Theoretically, dronedarone might share the latter class effect, therefore since its launch on the market, close surveillance of thyroid ADRs has been performed by the Marketing Authorization Holder (MAH) via routine pharmacovigilance, namely in subsequent 6-month Periodic Safety Update Reports (PSURs). The Risk Management Plan updates coincident with the release of PSURs, refer to thyroid disorders as a potential class effect encouraging regular data review by the MAH. From periodic analyses of the cases reporting thyroid ADRs, the MAH has not confirmed an evidence of a causal link between dronedarone and thyroid disorders including hyperthyroidism. In the Assessment Report to the most recently submitted PSUR (September 2011) EMA endorsed the MAH conclusion on the topic.

From launch of dronedarone to 31 January 2012 the MAH has collected worldwide 34 post-marketing cases including the ADR hyperthyroidism. In most of them only biological abnormality was reported. Analysis of the 34 cases led to exclusion of 18 cases; two due to incompatible chronology, two TSH in favour of hypothyroidism, one iodine-rich contrast media use, one Basedow’s disease, three underlying hyperthyroidism with limited information and nine with overall insufficient documentation. In six additional cases pre-existing amiodarone-induced hyperthyroidism was reported without details on diagnosis, treatment or outcome. Other five cases reported previous use of amiodarone. The latter may trigger hyperthyroidism at least up to nine months post-withdrawal. When documented, amiodarone use in these cases extended from seven months to two years. The time-to-onset with regard to dronedarone start was of 6 to 13 months. For three cases a single previous normal value of thyroid hormones was stated. For none of the cases recovery or type of corrective treatment were stated. In four of the five remaining cases information on amiodarone exposure was unknown, while in one case it was denied. Time-to-onset in these cases ranged from three to five months. A single normal previous value of thyroid hormones was stated for two cases, in one of which it dated from one year before start of dronedarone. Complete diagnostic workup, corrective treatment and outcome were missing for all. For two cases only echographic findings were available, showing thyroid gland hypervascularization and enlarged multiheteronodular thyroid gland with zones of hyper and hypoactivity, respectively. In the only case where previous amiodarone use was denied, the patient, a 76-year-old woman was found with moderate hyperthyroidism during hospitalization for recurrence of atrial fibrillation after three months of dronedarone use. Dronedarone was discontinued. No further explorations or diagnostic tests were mentioned. Corrective treatment was not specified. This was the patient with apparently normal thyroid function one year before. Detailed medical history was not available. Concomitant use of alprazolam suggested a pre-existing anxiety. The case documentation elements were not sufficient in order to allow drawing a clear conclusion.

Relatively high prevalence of hyperthyroidism in the general population (0.5 – 2% in women and 10 times less in men in the Whickham survey confirmed by data of other population surveys), mainly elderly, and large worldwide use of dronedarone yielding low number of cases are to be noted. Moreover atrial fibrillation itself may result from baseline hyperthyroidism. Due to these confounding factors combined with lack of relevant information in post-marketing setting further discussion of the data was not possible.

Available preclinical and clinical MAH data are not supportive of dronedarone-induced hyperthyroidism.

When referring to thyroid changes observed with dronedarone in rats and dogs, they were absent (dog) or minor (rat) as compared to amiodarone-induced follicular hypertrophy and hyperplasia. No effect on TSH was noted in these species as compared to a significant effect of amiodarone. In placebo-controlled clinical trial program in the pooled population of close to 3000 patients per arm the incidence of patients with thyroid events including hyperthyroidism was comparable between dronedarone (1.5%) and placebo groups (1.3%). In the DIONYSOS study, an 84.2% relative risk reduction (p = 0.0006) for thyroid disorders was observed in the dronedarone group compared to amiodarone. Four patients receiving amiodarone developed hyperthyroidism versus none in the dronedarone group.

Based on available up-to-date information the MAH concludes that there is no evidence of a causal role of dronedarone in hyperthyroidism.
Mometasone and Arrhythmia
Ian Boyd, Australia

Summary
Mometasone is a synthetic corticosteroid with anti-inflammatory, antipruritic and vasoconstrictive properties, it is available in three dosage forms: topical, nasal spray and dry powder inhalation. In VigiBase™ there are currently (March 2012) 15 reports of arrhythmia and two reports of atrial arrhythmia in association with mometasone. The reports are from the United States, United Kingdom, Sweden and Switzerland. Mometasone had been withdrawn in ten cases and the reaction recurred on rechallenge in three of the cases. Case control studies have demonstrated an increased risk of atrial fibrillation (AF) in association with oral corticosteroid use and a mechanism has been proposed. The possibility of systemic reactions in association with intranasal, inhaled or topical corticosteroids is considered low but there has been one literature report of AF in association with fluticasone. Case reports in VigiBase suggest that there is a signal for the association of mometasone and arrhythmia.

Introduction
Mometasone is a synthetic corticosteroid with anti-inflammatory, antipruritic and vasoconstrictive properties. It is available in three dosage forms: topical, nasal spray and dry powder inhalation. The topical form is presented as a cream or lotion and is indicated for the short term relief of inflammatory and pruritic manifestations of corticosteroid responsive dermatoses, such as psoriasis and atopic dermatitis. Common adverse effects (AEs) of the topical preparations include skin reactions such as pruritus, burning, tingling, signs of skin atrophy and acneiform reactions. Other local reactions have also been reported less commonly. The nasal spray is available for treatment of allergic rhinitis, nasal polyps and rhinosinusitis. Systemic absorption is possible from the nasal spray although bioavailability is regarded as low. Common AEs of the nasal preparation include headache, epistaxis and nasal reactions. Other AEs include rare hypersensitivity reactions and disturbances of taste and smell. The dry powder inhalation is available for treatment of asthma, and oral candidiasis is a very common AE. Other common AEs include pharyngitis, headache and dysphonia. There is also potential for hypersensitivity reactions.

Arrhythmia refers to disturbances in normal cardiac rhythm. It includes a large and heterogeneous group of conditions which arise from abnormal electrical activity in the heart. Arrhythmias can range from minor, common "skipped beats" to life-threatening conditions. In general, arrhythmia can refer to disturbances in rate or rhythm but simple disturbances in rate such as bradycardia or tachycardia would usually be coded as such. Arrhythmias may be caused by many different factors including coronary artery disease, electrolyte imbalance, heart muscle disorders and as indicated above, may occur in "normal, healthy" hearts. A wide range of drugs has been implicated in the development of arrhythmias including antihistamines, sympathomimetics, methylxanthines, anticholinergic drugs, antiarrhythmic drugs and a variety of other drugs including cisapride and erythromycin.

Reports in VigiBase
As of March 2012 there are 15 individual case safety reports (ICSRs) of arrhythmia and two ICSRs of atrial arrhythmia in association with mometasone in the WHO Global ICSR database, VigiBase™. One report was excluded from the analysis as it was a neonatal with congenital heart disease which leaves 16 reports in total. It should be noted that these associations were generated using a different signal identifying process which relies on the Lasso Logistic Regression value and does not require the IC025 to be positive. The reports were submitted from the US (13 cases), the UK, Sweden and Switzerland (one case each). The patients ranged in age from 12 to 79 years with a median of 57 years in the 12 cases in which this information was provided. In the 14 cases which provided the information, the gender distribution was relatively even with 6 males and 8 females. Noteworthy is that six reports were consumer reports. Out of the rest of the reports one had no reporter type listed and nine reports came from physicians, pharmacists and other health care professionals.
Table 1. Overview of reports in VigiBase™ for mometasone associated with arrhythmia and arrhythmia atrial.

<table>
<thead>
<tr>
<th>Case</th>
<th>Age/Gender</th>
<th>Reactions (MedDRA preferred terms)</th>
<th>Other suspected (S) or concomitant (C) drugs</th>
<th>Dechallenge, Rechallenge and Outcome</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>12/F</td>
<td>Angina pectoris, arrhythmia</td>
<td>Methylphenidate (C)</td>
<td>Pos dechallenge</td>
<td>History of Wolff-Parkinson-White syndrome, no episodes for six years. The reporter considers the event unlikely related to mometasone.</td>
</tr>
<tr>
<td>2</td>
<td>/-</td>
<td>Arrhythmia</td>
<td>None</td>
<td>Pos dechallenge</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>74/M</td>
<td>Arrhythmia, dizziness, headache, vertigo, vomiting</td>
<td>Fexofenadine, metformin, glimepiride, ranitidine, acetyl salicylic acid, phsyllium seed husk, verapamil hydrochloride, digoxin, latanoprost, brimonidine (all C)</td>
<td>Pos dechallenge</td>
<td>History of arrhythmia Had a vertigo that was so bad that he started to vomit which caused the heart to go out of sinus rhythm</td>
</tr>
<tr>
<td>4</td>
<td>79/F</td>
<td>Tachycardia, sick sinus syndrome, pneumothorax (after insertion of pacemaker), palpitation, haemoptysis, epistaxis, atrioventricular block, fibrillation atrial</td>
<td>Oxygen (S) Blinded study drug (S) Acetylsalicylic acid, fluticasone propionate/salmeterol xinafoate, levotiroxine, lansoprazole, famotidine, netoprolol, ergocalciferol, calcium (all C)</td>
<td>Recovered with sequelaes</td>
<td>The patient took part in a blinded zolendronate study, study medication was listed as suspect</td>
</tr>
<tr>
<td>5</td>
<td>64/F</td>
<td>Arrhythmia, hypertension, vertigo, chest pain</td>
<td>Tacalcitol (S)</td>
<td>Drug withdrawn Recovered</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>/-M</td>
<td>Arrhythmia, heart disorder</td>
<td>None</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>/-F</td>
<td>arrhythmia atrial, extrasystoles</td>
<td>None</td>
<td>Pos dechallenge</td>
<td>Her medical doctor and Cardiologist believed that the event was not related to the drug</td>
</tr>
<tr>
<td>8</td>
<td>57/M</td>
<td>Arrhythmia, ecg abnormal, extrasystoles</td>
<td>None</td>
<td>Pos dechallenge</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>33/M</td>
<td>Extrasystoles, palpitation, arrhythmia atrial,</td>
<td>None</td>
<td>Pos dechallenge</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>75/F</td>
<td>Tachycardia, fibrillation atrial, hypokalaemia</td>
<td>Tramadol(S) Ergocalciferol, amiodopine, estradiol, mometasone* (all C)</td>
<td>Pos dechallenge for tramadol Recovered</td>
<td>The primary reporter does not mention mometasone as suspected but as a medication at the time of the event</td>
</tr>
<tr>
<td>11</td>
<td>41/F</td>
<td>Arrhythmia, fatigue, depression, cortisol decreased</td>
<td>None</td>
<td></td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>64/F</td>
<td>Arrhythmia, malaise, palpitation</td>
<td>Magnesium, calcium, plantago ovata/ispaghula husk (all C)</td>
<td>Recovered from palpitations and malaise.</td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>25/M</td>
<td>Arrhythmia</td>
<td>None</td>
<td>Pos dechallenge Recovered</td>
<td></td>
</tr>
<tr>
<td>14</td>
<td>57/M</td>
<td>Arrhythmia, extrasystoles,</td>
<td>None</td>
<td>Pos dechallenge Pos</td>
<td></td>
</tr>
<tr>
<td>ID</td>
<td>Age</td>
<td>Symptoms</td>
<td>Rechallenge</td>
<td>Outcome</td>
<td></td>
</tr>
<tr>
<td>----</td>
<td>-----</td>
<td>-----------------------------------</td>
<td>-------------</td>
<td>------------------------------</td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>38/F</td>
<td>Arrhythmia, insomnia, dysgeusia,</td>
<td>Pos dechallenge</td>
<td>Patient hospitalised for panic attack</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>ageusia hypoesthesia, tachycardia, anxiety, agitation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>16</td>
<td></td>
<td>Arrhythmia</td>
<td>Pos dechallenge</td>
<td>Recovered</td>
<td></td>
</tr>
</tbody>
</table>
Mometasone was the only drug suspected in 13 cases and only three of these listed concomitant drugs. One of the remaining three cases had one co-suspected drug, one case had two other suspected drugs and in case 10 it was shown on the original report that the reporter had listed mometasone as a concomitant drug. Out of the cases that listed concomitant drugs there was no pattern in the drugs reported as concomitant apart from the occasional use of vitamins, minerals and calcium. Mometasone was administered intranasally in the majority (13) of the cases with two reports of inhalation and one of topical use.

Time to onset was reported in only three of the reports and ranged from the same day up to three months. The duration of use was recorded in three additional reports and was three to four days in two cases and two months in another. A positive dechallenge from mometasone was recorded in nine cases. The indication for use of mometasone was reported in ten cases and included allergic conditions or nasal polyps in eight cases, psoriasis in the case where mometasone was used topically and asthma in one of the cases of inhalational use.

As noted in Table 1, the reported reaction was unspecified arrhythmia in 12 cases and tachycardia, heart rate abnormal and extrasystoles in the remaining cases. Eight of the cases reported more than one term relating to arrhythmia such as palpitations, atrial fibrillation, sick sinus syndrome and atrioventricular block. Some of these terms were also reported by themselves as reactions to mometasone or in combination with other heart rate related terms than arrhythmia, but these reports were not included in this analysis. Three patients had a past history of arrhythmia. In case 1 the patient had a history of Wolff-Parkinson-White syndrome but had not had any symptoms for six years when after three days of mometasone use the patient experienced arrhythmia. In case 3 arrhythmia was included in the patient’s medical history without further explanations and in case 13 the patient had occasional extra heart beats that increased strongly when mometasone was administered and disappeared upon removal of the drug.

The same thing happened when trying to use the drug 6 months later. Four cases in total, reported that the reaction recurred on rechallenge.

**Literature and Labelling**

The product literature for mometasone does not refer to arrhythmia. As noted above, bioavailability is regarded as low from the nasal spray which has been implicated with the majority of the reports. The product information also notes that systemic effects were not detected in adults, adolescents or children following the administration of mometasone aqueous nasal spray. Oteri and colleagues reported the development of a paroxysmal atrial fibrillation (AF) with fast ventricular response after the administration of a different inhaled corticosteroid, fluticasone propionate, to a 15 year old boy, which resolved after discontinuation of the drug. The patient had a history of allergic asthma and had been treated for several years with cetirizine and inhaled mometasone to treat seasonal allergic rhinitis. The authors noted that corticosteroid-induced AF had previously been reported in three case control studies. Huerta et al. reported a twofold increased risk of AF among users of oral corticosteroids compared with nonusers. Conversely, no increased risk was found among users of inhaled corticosteroids. The results of a large population-based case control study, conducted in Denmark, showed an almost doubled risk of AF or flutter associated with systemic corticosteroid use, with respect to nonuse, in patients with and without chronic obstructive pulmonary disease or asthma and cardiovascular diseases. Van der Hooft also reported an increase in the risk of AF among users of systemic corticosteroids in a study which involved 385 cases of AF from the Netherlands. It has been postulated that high doses of corticosteroids mediate potassium efflux via a direct effect on the cell membrane, which may induce arrhythmogenesis.

**Discussion and Conclusion**

The existing literature with regard to corticosteroid use and arrhythmia is rather limited and consists of some case reports that refer to systemic methylprednisolone but not to inhaled corticosteroids. There has been one literature report of AF in association with fluticasone propionate by the inhalation route and case control studies have shown an increased risk of AF in association with oral corticosteroids. A postulated mechanism by which corticosteroids can cause heart rate disorders involves potassium efflux in cardiac cells.

It is generally accepted that systemic effects of corticosteroids are considerably less likely with inhaled or intranasal administration but it is possible that these effects may occur in susceptible individuals.

However, there have been no reports in the literature implicating arrhythmias for mometasone. Case reports in VigiBase suggest that there is a signal for the association of mometasone and arrhythmia. Most of the cases have mometasone as the sole suspected drug and a positive dechallenge, supporting a signal. In the few reports that describe the time to onset, it is consistent with a drug-induced effect. Importantly, in four of the cases, the reaction recurred on rechallenge.
Response from MAH, MSD, regarding a signal of mometasone and Arrhythmia

We have reviewed these documents.

All reports of arrhythmia, including atrial fibrillation, for mometasone products (oral, nasal, topical) will be included in the list of closely monitored adverse events.

Medical assessment of reports with the adverse events of arrhythmia will be provided in the upcoming 3-year PSUR, 23-May-2009 to 22-May-2012.
CAVEAT DOCUMENT

Accompanying statement to data released from the Uppsala Monitoring Centre, WHO Collaborating Centre for International Drug Monitoring

Uppsala Monitoring Centre (UMC) in its role as the WHO Collaborating Centre for International Drug Monitoring receives reports of suspected adverse reactions to medicinal products from National Centres in countries participating in the WHO pharmacovigilance network, the WHO Programme for International Drug Monitoring. Limited details about each suspected adverse reaction are received by the UMC. The information is stored in the WHO Global Individual Case Safety Report database, VigiBase. It is important to understand the limitations and qualifications that apply to this information and its use.

The reports submitted to UMC generally describe no more than suspicions which have arisen from observation of an unexpected or unwanted event. In most instances it cannot be proven that a specific medicinal product (rather than, for example, underlying illness or other concomitant medication) is the cause of an event.

Reports submitted to National Centres come from both regulated and voluntary sources. Some National Centres accept reports only from medical practitioners; other National Centres accept reports from a broader range of reporters, including patients. Some National Centres include reports from pharmaceutical companies in the information submitted to UMC; other National Centres do not.

The volume of reports for a particular medicinal product may be influenced by the extent of use of the product, publicity, the nature of the reactions and other factors. No information is provided on the number of patients exposed to the product.

Some National Centres that contribute information to VigiBase make an assessment of the likelihood that a medicinal product caused the suspected reaction, while others do not.

Time from receipt of a report by a National Centre until submission to UMC varies from country to country. Information obtained from UMC may therefore differ from those obtained directly from National Centres.

For the above reasons interpretations of adverse reaction data, and particularly those based on comparisons between medicinal products, may be misleading. The supplied data come from a variety of sources. The likelihood of a causal relationship is not the same in all reports. Any use of this information must take these factors into account.

Some National Centres strongly recommend that anyone who intends to use their information should contact them for interpretation.

Any publication, in whole or in part, of information obtained from UMC must include a statement:

(i) regarding the source of the information,
(ii) that the information comes from a variety of sources, and the likelihood that the suspected adverse reaction is drug-related is not the same in all cases,
(iii) that the information does not represent the opinion of the World Health Organization.

Omission of this statement may exclude the responsible person or organization from receiving further information from VigiBase.

2011
Paediatric morphine dosages

W Scholten, Essential Medicines and Health Products, WHO

New dosage recommendations are now available in the WHO Guidelines on the Pharmacological Treatment of Pain in Children with Medical Illnesses, published earlier in 2012\(^1\). The new Guidelines have a more cautious approach and replace the dosage recommendations in the WHO Model Formulary for Children (2010)\(^2\). In view of these new Guidelines the dosage recommendations for morphine and other opioid analgesics in children in future editions of other relevant publications (textbooks, handbooks etc.) may need to be reconsidered. WHO has no recently published guidelines on the use of opioid analgesics in adults, but the following may also apply to their prescription to adults:

Pain treatment with strong opioids should be based on a low initial dosing. (See tables 1 to 3 for paediatric starting dosages.) Titration of the dosage should be based on a regular assessment of the pain level. This assessment is discussed in the Guidelines. After a starting dose according to the Guidelines, the dosage should be adjusted to the level that is effective (with no ceiling or maximum dose), but the maximum dosage increase is 50% per 24 hours in outpatient settings. Experienced prescribers can increase up to 100% with close monitoring of the patient, increasing to the level that is effective. The preferred route is oral. If oral administration is not possible, subcutaneous administration or other parenteral routes can be considered, but intramuscular administration should be avoided as it is painful. It should be noted that, due to the first pass effect, parenteral administration is about twice as potent as oral administration.

The dose titration schedule mentioned above also applies to most other strong opioids as well, but not to methadone because of its long half-life. Details for titrating methods for methadone that avoid accumulation can be found in the Guidelines.

In case of overdosage of opioids, the antagonist naloxone can be administered.

Occurrence of dependence is often not well understood. On adequate treatment of pain, it is rare, if occurring at all. However, if opioids are withdrawn abruptly in chronic treatment, severe withdrawal symptoms will be precipitated. Therefore, when stopping treatment, the patient should be weaned gradually: after short-term therapy (7-14 days), the dose can be decreased by 10–20% of the original dose every 8 hours, increasing gradually the time interval between doses. After long-term therapy, the dose should be reduced not more than 10–20% per week.

Pharmacological profiles for morphine and several other opioid and non-opioid analgesics, as well as for the antagonist naloxone can be found in Annex 1 of the Guidelines (page 63). The Guidelines can be downloaded from the web free of charge. The printed Guidelines package contains also a pocket dosing card and pain assessment scales for children.

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### Table 1. Starting dosages for opioid analgesics for opioid-naive neonates

<table>
<thead>
<tr>
<th>Medicine</th>
<th>Route of administration</th>
<th>Starting dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine</td>
<td>IV injection&lt;sup&gt;a&lt;/sup&gt;</td>
<td>25–50 mcg/kg every 6 hrs</td>
</tr>
<tr>
<td></td>
<td>SC injection</td>
<td></td>
</tr>
<tr>
<td></td>
<td>IV infusion&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Initial IV dose&lt;sup&gt;a&lt;/sup&gt; 25–50 mcg/kg, then 5–10 mcg/kg/hr</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>IV injection&lt;sup&gt;b&lt;/sup&gt;</td>
<td>1–2 mcg/kg every 2–4 hrs&lt;sup&gt;2&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>IV infusion&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Initial IV dose&lt;sup&gt;c&lt;/sup&gt; 1–2 mcg/kg, then 0.5–1 mcg/kg/hr</td>
</tr>
</tbody>
</table>

<sup>a</sup> Administer IV morphine slowly over at least 5 minutes.

<sup>b</sup> The intravenous doses for neonates are based on acute pain management and sedation dosing information. Lower doses are required for non-ventilated neonates.

<sup>c</sup> Administer IV fentanyl slowly over 3–5 minutes.

### Table 2. Starting dosages for opioid analgesics in opioid-naive infants (1 month–1 year)

<table>
<thead>
<tr>
<th>Medicine</th>
<th>Route of administration</th>
<th>Starting dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine</td>
<td>Oral (immediate release)</td>
<td>80–200 mcg/kg every 4 hrs</td>
</tr>
<tr>
<td></td>
<td>IV injection&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1–6 months: 100 mcg/kg every 6 hrs 6–12 months: 100 mcg/kg every 4 hrs (max 2.5 mg/dose)</td>
</tr>
<tr>
<td></td>
<td>SC injection</td>
<td></td>
</tr>
<tr>
<td></td>
<td>IV infusion&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1–6 months: Initial IV dose: 50 mcg/kg, then: 10–30 mcg/kg/hr 6–12 months: Initial IV dose: 100–200 mcg/kg, then: 20–30 mcg/kg/hr</td>
</tr>
<tr>
<td></td>
<td>SC infusion</td>
<td>1–3 months: 10 mcg/kg/hr 3–12 months: 20 mcg/kg/hr</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>IV injection&lt;sup&gt;b&lt;/sup&gt;</td>
<td>1–2 mcg/kg every 2–4 hrs&lt;sup&gt;2&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>IV infusion</td>
<td>Initial IV dose 1–2 mcg/kg&lt;sup&gt;c&lt;/sup&gt;, then 0.5–1 mcg/kg/hr</td>
</tr>
<tr>
<td>Oxycodone</td>
<td>Oral (immediate release)</td>
<td>50–125 mcg/kg every 4 hours</td>
</tr>
</tbody>
</table>

<sup>a</sup> Administer IV morphine slowly over at least 5 minutes.

<sup>b</sup> The intravenous doses of fentanyl for infants are based on acute pain management and sedation dosing information.

<sup>c</sup> Administer IV fentanyl slowly over 3–5 minutes.
Table 3. Starting dosages for opioid analgesics in opioid-naive children (1–12 years)

<table>
<thead>
<tr>
<th>Medicine</th>
<th>Route of administration</th>
<th>Starting dose</th>
</tr>
</thead>
</table>
| Morphine      | Oral (immediate release) | 1–2 years: 200–400 mcg/kg every 4 hrs  
2–12 years: 200–500 mcg/kg every 4 hrs (max 5 mg) |
|               | Oral (prolonged release)| 200–800 mcg/kg every 12 hrs                       |
|               | IV injection a          | 1–2 years: 100 mcg/kg every 4 hrs  
2–12 years: 100–200 mcg/kg every 4 hrs (max 2.5 mg) |
|               | SC injection            | Initial IV dose: 100-200mcg/kg a, then  
20–30 mcg/kg/hr                                   |
|               | IV Infusion             | 20 mcg/kg/hr                                      |
|               | SC Infusion             | 20 mcg/kg/hr                                      |
| Fentanyl      | IV injection            | 1–2 mcg/kg b, repeated every 30–60 minutes        |
|               | IV Infusion             | Initial IV dose 1–2 mcg/kg b, then 1 mcg/kg/hr    |
| Hydromorphone | Oral (immediate release) | 30–80 mcg/kg every 3–4 hrs (max 2 mg/dose)        |
|               | IV injection d or SC injection | 15 mcg/kg every 3–6 hrs                          |
| Methadone     | Oral (immediate release) | 100–200 mcg/kg every 4 hrs for the first 2–3 doses, then every 6–12 hrs (max 5 mg/dose initially) f |
|               | IV injection p and SC injection |                                                 |
| Oxycodone     | Oral (immediate release) | 125–200 mcg/kg every 4 hours; max 5 mg/dose       |
|               | Oral (prolonged release)| 5 mg every 12 hours                               |

a Administer IV morphine slowly over at least 5 minutes.
b Administer IV fentanyl slowly over 3–5 minutes.
c Hydromorphone is a potent opioid and significant differences exist between oral and intravenous dosing. Use extreme caution when converting from one route to another. In converting from parenteral hydromorphone to oral hydromorphone, doses may need to be titrated up to 5 times the IV dose.
d Administer IV hydromorphone slowly over 2–3 minutes.
e Due to the complex nature and wide inter-individual variation in the pharmacokinetics of methadone, methadone should only be commenced by practitioners experienced with its use.
f Methadone should initially be titrated like other strong opioids. The dosage may need to be reduced by 50% 2–3 days after the effective dose has been found to prevent adverse effects due to methadone accumulation. From then on dosage increases should be performed at intervals of one week or over and with a maximum increase of 50%.
g Administer IV methadone slowly over 3–5 minutes.
Ninth meeting of the WHO Advisory Committee on Safety of Medicinal Products

3-4 May 2012, Geneva

The WHO Advisory Committee on Safety of Medicinal Products (ACSoMP) has been constituted to provide advice on pharmacovigilance (PV) policy and issues related to the safety and effectiveness of medicinal products. Following is a summary of discussions and recommendations from the ninth meeting.

PV toolkit

The Pharmacovigilance Toolkit is intended as a pharmacovigilance (PV) resource repository for low and middle income countries. The WHO Collaborating Centre for Advocacy and Training in Pharmacovigilance, Ghana has been leading the work on the Toolkit, with support from the WHO and the UMC. The toolkit has been presented to the Committee at its previous meetings and has received valuable comments and guidance from the members. The toolkit was launched on January 2012 and has generated wide interest globally, and feedback from users of the web toolkit has been positive. Both web accessible (www.pvtoolkit.org) and available in thumb drives, this resource also includes material from public health programmes.

At the ninth meeting, the ACSoMP advised that the toolkit should include links to other publications such as the European guideline on good pharmacovigilance practices as well as consider translating the toolkit content into other languages, for broader uptake and ease of use.

Procedures for reviewing safety concerns by ACSoMP

This topic was considered in the light of recent drug scares around the world when WHO was called upon to provide urgent technical and strategic assistance to the affected countries. The committee discussed a proposal that outlined the process by which safety concerns are channelled to WHO and action steps that follow this, including how members of the advisory committee can be engaged in the investigations. Communications, documentation and knowledge management protocols were suggested. It was agreed that WHO should put together a list of PV professionals highlighting their competent expertise; and that this list could be referred to when identifying relevant experts to handle and investigate the crises.

EU PV legislation and reports from EU Member States

The Committee discussed the new EU PV legislation and the potential impact on the WHO Programme for International Drug Monitoring. The WHO Programme was established in 1968, in response to the thalidomide disaster, to collect, analyse and share information on adverse drug events globally. The EU member states are important partners in this collaboration. The Committee reaffirmed the vital value of VigiBase, the WHO global Individual Case Safety Reports (ICSR) database as a global signal detection tool, and the need for all countries in the WHO Programme to ensure that the best possible data quality is provided whilst adhering to applicable country laws and regulations for the protection of patient confidentiality. The Committee recommended that a working group should be established, to work with the EMA, to ensure and facilitate the continuing collaboration with EU Member States, for meaningful data exchange between WHO and EU states, to support WHO in its mandate of detecting signals and providing global information on drug safety in a timely fashion.
Detecting, analysing and preventing medication errors within PV centres

This session referred to one of the outputs of an ongoing WHO project with various partners under the Seventh Framework Programme of the European Union (EU-FP7). This aspect of the project aims to increase the capacity of PV centres in identifying and understanding the root causes of preventable ADRs. A draft publication ‘Reporting and learning systems for medication errors: detecting, analysing and preventing within pharmacovigilance centres’ has been prepared by WHO, together with the Morocco PV Centre, National Patient Safety Alliance, UK and the UMC. The broad elements of the draft were presented to ACSoMP at its ninth meeting.

In the US FDA, medication error (ME) prevention work is incorporated within drug development of the industry, which includes an assessment of proprietary names of the medicinal products, among others. In China, while MEs are in the purview of the ministry of health, the PV centres do receive reports. The Committee noted that off-label use of medicines leading to harmful outcomes must be responsibly reported but this is not undertaken currently and lessons are lost. Therefore, a proposal to map the impact of harm from MEs was made. WHO was advised to send the document for public comments.

PV of medicines supplied through international agencies

In assisting countries to treat priority diseases, international agencies often procure and supply medicines to countries with little or no functional PV systems; marketing authorization holders (MAH) with regulatory requirements to collect reports on these products are often unable to meet this responsibility in these settings. This is particularly true when the products are put to off-label use. The Committee reviewed a PV agreement that would be signed by countries as a condition to receiving cheaper medicines in a specific disease treatment programme. Obligations of each party in the drug procurement and supply chain are stipulated in the agreement with clearly defined responsibility for PV within this collaboration.

The Committee noted that the proposed agreement is not explicit on the accountability of the responsible agency within the recipient country for PV monitoring, responsibility for addressing serious drug reactions, nor the legal role of national regulatory authorities (NRAs). The Committee also advised that:

- risk communication needs to be included in the agreement because serious adverse events (SAE) like cardiac and hepatic deaths can damage the reputation and credibility of public health programmes
- roles of public health departments, the NRAs, the PV centres and the recipient organizations should be better clarified in the agreement.

The Committee recommended a coordinated effort, at a higher level within WHO, for a responsible, consistent, and standard plan with an organization-wide strategy to integrate PV within all its drug administration programmes.

Definitions in PV

The Committee discussed the normative role of WHO in establishing definitions and recommended that WHO should continue developing definitions in pharmacovigilance as the recognized authority in providing a common framework. But it is necessary to include the perspectives and inputs from industry as important stakeholders. The Committee approved that the Council for International Organizations of Medical Sciences (CIOMS) consultation meetings on PV definitions is a good model for facilitating discussions with industry.

Safety of medicines in sub-Saharan Africa: USAID- SPS

A recent survey of selected African countries by the USAID/Strengthening Pharmaceutical Systems (SPS) programme highlights the lack of capacity to monitor drug safety, the inadequate PV policies and their implementation in the region. Results show that although many countries have PV programs, the functionalities are quite variable, especially with respect to electronic information exchange, and the ability to take actions on Signals. While 70% of global population on anti-retroviral medicines live in Africa, only 6% of ADR reports come from Africa. The survey concluded with a number of policy recommendations related to infrastructure for strengthening PV, risk management planning, integration of PV into training and education, using safety data in regulatory decisions and treatment guidelines. The Committee noted the synergies with recommendations from similar surveys by WHO and suggested collaborations between WHO and SPS for joint strategies and solutions to the identified challenges, and their implementation in countries.
PV of TB
The global burden of TB is considerably high (9M cases in 2010, with 1M deaths, 650,000 cases of MDR TB). XDR TB cases have been reported worldwide. Some countries have no laboratory capacity to detect XDR which contributes to underreporting. While TB drugs have been in the market for long and ADRs are known, the extent of ADR related morbidities and mortalities are unknown. Part of the problem appears to be the long treatment and complex regimen, and the presence of co-morbidities; with the scale up of treatment and the introduction of new TB drugs worldwide, care must be taken to prevent resistance to the new TB drugs.

Targeted Spontaneous Reporting (TSR), WHO’s approach for collecting ADR data in public health programmes, is well suited for PV in TB control programmes in low resource settings and builds on integrating safety monitoring as part of a national TB treatment programme. ADRs will be monitored as standard of care in DOTS (direct observed treatment), to collect information on specific adverse events and / or specific treatment regimens. The Committee noted that while TSR provides a practical tool, for integrating PV within a public health programme, it will be challenging to detect new and unexpected reactions with this approach.

Monitoring Medicines (MM) project
The EC-funded Monitoring Medicines project was developed by WHO and is currently being implemented as a partnership of 11 countries and coordinated by the UMC. The broad objectives are to support and strengthen consumer reporting and to expand the role and scope of work of PV centres to include MEs. This will lead to broader & efficient use of existing PV data. Analysis of VigiBase to provide better indicators for detecting dependence producing medicines and developing methods to detect incidence of substandard medicines are two such examples of this work. Moreover, the project also intends to develop additional PV methods to complement spontaneous reporting. There is a further component to develop learning tools for PV for HIV treatment managers. Various work packages, the activities and products that were produced from the work packages were presented. The Project will be completed by Feb 2013.

The Committee recommended that the web based tool for ADR reporting by patients that has been developed under the MM project initiative should be shared with the EMA for further development of the tool and for its possible use within EU. The Committee advised the wider dissemination of the MM project results at the PV side event at the 65th World Health Assembly at Geneva, in May 2012.

Toxicity monitoring in routine antiretroviral therapy (ART) implementation
The key interest of PV monitoring in ART is to find local toxicity cases that can inform global and national treatment guidelines. TSR is being introduced in ART in Kenya, and Cote d'Ivoire, Vietnam and Laos, and Cohort Event Monitoring (CEM) is about to be launched in ART in Tanzania. The Committee discussed key toxicities related to ARVs: renal toxicity with tenofovir, risk of teratogenicity with efavirenz, hypersensitivity reactions to nevirapine.

Safety of antimalarials
Amodiaquine (AQ) was removed several years ago from the WHO Model List of Essential Medicines but was later re-introduced in combination with artesunate (AS), for the treatment of uncomplicated falciparum malaria. Following Zanzibar and Burundi, Ghana was among the first countries in Africa to introduce this combination as 1st-line treatment of malaria and adverse reactions were reported with this combination in the country through both hospital studies and spontaneous reports to the national pharmacovigilance centre. A review commissioned by WHO found a causal association between the drug combination and movement disorders, and concluded that this is a Signal. Based on these findings, the MAH was asked to review its Summary of Product Characteristics (SPC), to include the newly reported side effects.

In a revised SPC, the MAH proposes to include the observations of both dystonia and extra pyramidal symptoms. The committee recommended that in addition to withholding treatment in case of appearance of such reactions, proper guidance should be given to health workers for pro-active management of dystonic reactions and that advice on use of suitable alternative medicines to treat malaria should be provided. The Committee also recommended that the SPC should provide clarity on dosing in children and should be re-written, so that it is easily understood by laypersons. The Committee also made other recommendations with edits on specific sections of the SPC, to be conveyed to the MAH.
Piloting PV indicators in selected countries

The WHO PV indicators have been developed as quality assurance tools for the evaluation, comparison and trending of PV systems and practice in countries. The indicators cover core and complementary parameters as well as structure, process and outcome matrices and will support the collection of both quantitative and qualitative data. The WHO PV indicators will be implemented, in 2-3 countries per region; two health-care facilities and one public health program will be included per country in the pilot.

The Committee noted that there are currently no standards for PV centres which can be used as benchmark for objective comparisons. The Committee acknowledged that complete data collection will not be possible in certain settings, but at the very least, these PV indicators are educational tools for NCs to appreciate process, progress and outcomes. There is also a predictive value to the indicators, that allows NCs to prepare themselves for the future: for example, measurements of increasing ADR reports would alert NCs to practical implications (of such trends) on human resources, staff training and funding of PV centres. The Committee recommended that the current version of the WHO PV indicators should be published on the WHO medicines website and included in the WHO PV toolkit; the Committee also recommended collaborating with the WHO Global Vaccine Safety initiative on the revision of the vaccine vigilance indicators.

Global Vaccine Safety (GVS) initiative

The GVS initiative was first presented to ACSoMP at its eighth meeting, in 2011. This initiative is to strengthen global capacity for vaccine PV, has been endorsed by the Strategic Advisory Group of Experts (SAGE) on Immunization and Global Advisory Committee on Vaccine Safety (GACVS) and is aligned with the Decade of Vaccines Collaboration that focuses on improving global vaccine strategies. There are 8 strategic objectives. WHO acts as the secretariat and there is a governance steering committee to ensure strategic execution of the objectives. The GVS initiative will be presented at the 65th World Health Assembly (WHA) for approval.

Initial implementation has been undertaken through existing mechanisms (vaccine PV networks, WHO Collaborating Centres and CIOMS, with progress reports to SAGE and GACVS), with diverse financing. The Committee also heard about present developments to VigiFlow, to make it more user friendly for AEFI (Adverse Events Following Immunization) data entry. The vaccine-friendly version of VigiFlow (the ADR data management tool) will be called VacciFlow. The Committee approved the initiative but cautioned that care is needed, to ensure that VigiFlow and VacciFlow are not perceived to be two different systems.

WHO SSFFC Global Surveillance and Monitoring Project

SSFFC stands for ‘Substandard, spurious, falsely labelled, falsified and counterfeit’ medicines. SSFFC case studies were presented by the relevant WHO team that is leading this project, to elucidate examples of:

- Commercial diversion and falsely labelled products
- Intention to deceive – with no active pharmaceutical ingredient (API) or ‘actives’ in products
- Substandard products with specific contaminants
- Reduced amount of API in products
- Quality problem with clear intention to deceive (for example, 99% ‘actives’ detected but failure to dissolve)
- Manufacturing error with contamination.

Raising awareness of the issue, whilst important, must be dealt with carefully to avoid the unintended consequence of assisting those engaged in this illicit activity to improve production of their dangerous products. There is much misleading information about the scale and scope of SSFFC medical products. The project will thus encourage Member States to report incidents to the WHO in a systematic manner providing a reliable body of evidence by which to make future decisions and arrive at an accurate assessment of threat.

Pilot studies in two regions - Europe and Western Pacific - have been proposed. The pilot study aims to establish a system for rapid reporting, and assessment of SSFFCs and to issue alerts. The Committee discussed the role of the WHO Medicines Safety programme and the UMC and how existing processes and tools can be used to the advantage of the SSFFC project. As a first step in this collaboration, the UMC will develop a real-time algorithm to data-mine Vigibase (the WHO global database of Individual Case Safety Reports) to compare against products known to be vulnerable to falsification.
Reporting of drug ineffectiveness

As a follow up of the conclusions from the 8th ACSoMP meeting, a working group from within the ACSOMP has proposed recommendations on reporting and assessing drug ineffectiveness. The group presented the importance of reporting therapeutic failure, and the wider use of the term to describe this adverse event. There are several reasons and mechanisms why a drug may not be effective at all or not as effective as expected in a particular case or cases (disease and patient-related, primary or secondary drug ineffectiveness, medication error, biopharmaceutical problems, substandard or counterfeit products, or new characteristics of disease). For a better assessment of drug ineffectiveness, the report should include some specific information about the patient, disease, other medications and other aspects of treatment and the description of medicine ineffectiveness. Due to specific mechanisms and public health relevance of unexpected drug ineffectiveness, the reasons for therapeutic failure in those instances need to be captured. The Committee observed that a separate system for reporting therapeutic ineffectiveness should not be proposed, but available reporting formats should be optimized, together with a guideline for reporting this kind of information. The Committee recommended integrating the necessary information fields (for better identification of therapeutic failure) in the ADR reporting form; developing a guideline to encourage and improve the quality of reports; and advancing these efforts in the context of drug resistance or other public health challenges.