WHO PHARMACEUTICALS NEWSLETTER

prepared in collaboration with the
WHO Collaborating Centre for
International Drug Monitoring,
Uppsala, Sweden

The aim of the Newsletter is to disseminate information on the safety and efficacy of pharmaceutical products, based on communications received from our network of "drug information officers" and other sources such as specialized bulletins and journals, as well as partners in WHO. The information is produced in the form of résumés in English, full texts of which may be obtained on request from:

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

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

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

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In this issue of the Newsletter we bring you a feature on a workshop on pharmacovigilance for countries in the West African region that was recently held in Accra, Ghana. The purpose of the workshop was to help countries in the region develop pharmacovigilance programmes where they do not exist and for strengthening existing programmes. Read more about the workshop in the 'Feature article'.

In addition to the regular information about Regulatory Matters and Safety of Medicines, the Newsletter gives you an article about collaborative participation of inspectors from national Medicines Regulatory Authorities (MRAs) in inspections coordinated by the WHO Prequalification of Medicines (PQM) Programme. The purpose of this strategy is better involvement of inspectors from MRAs of developing countries, and other interested Member States, in inspections organized by the WHO-PQM and training of inspectors from these countries.

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Safety of Medicines

Feature

Bufexamac

Revocation of marketing authorizations recommended because of high risk of contact allergies

Europe. The European Medicines Agency's Committee for Medicinal Products for Human Use (CHMP) has recommended that marketing authorisations for bufexamac-containing medicines be revoked throughout the European Union (EU). Bufexamac is a non-steroidal anti-inflammatory drug (NSAID) that is used as topical formulations to treat dermatological diseases (eczema and dermatitis) and proctological conditions (haemorrhoids and anal fissure).

The Committee conducted a review of the safety and effectiveness of bufexamac. The risk of developing a contact allergic reaction to bufexamac is high, and the risk is even higher in patients with pre-disposing conditions, such as certain forms of eczema, for which bufexamac is frequently prescribed. The allergic reactions can be serious enough to require hospitalization. The CHMP also noted that bufexamac causes reactions to get worse with repeated exposure. Furthermore, because the allergic reactions caused by bufexamac are very similar to the disease being treated, it can lead to delays in the diagnosis or treatment of the patient's condition. It is also likely that the difficulty to differentiate between a treatment failure and an allergic reaction has led to the cases of contact allergic reaction being underreported. In addition to this, the data to support the effectiveness of bufexamac are very limited.

Based on the available information, the CHMP concluded that the benefits of the bufexamac-containing medicines did not outweigh its risks and therefore recommended that they be taken off the market across the EU. Doctors are advised to stop prescribing medicines containing bufexamac; alternative anti-inflammatory treatments are widely available.

Reports in WHO Global ICSR database, Vigibase:

Bufexamac

Total number of reports: 648

Most reported reactions (number of events):

Bullous eruption	*24*
Pruritus	*73*
Dermatitis	*24*
Eczema	*215*
Dermatitis contact (contact allergy)	*216*
Rash	*32*
Rash erythematous	*97*
Rash maculo-papular	*27*
Urticaria	*32*

Reference:
Press release, Questions and answers, EMA, 22 April 2010 (www.ema.europa.eu).

Drospirenone-containing combined oral contraceptive

Update on the risk of venous thromboembolism

UK. The MHRA has provided an update on the risk of venous thromboembolism (VTE) in association with the combined oral contraceptive containing drospirenone (Yasmin). According to the Drug Safety Update, recently published studies suggest that the risk of VTE associated with Yasmin may be slightly higher than previously estimated, and somewhere between the risk associated with combined pills containing levonorgestrel (known as 'second generation') and those containing desogestrel or gestodene (known as 'third generation'). The Agency adds that because of some limitations in the methodology of these recent studies, further analyses are needed before any firm conclusions can be drawn. In the meantime, prescribers are advised to be aware of the new evidence when discussing the most suitable type of contraceptive for any woman who wants to start or switch contraception.

In addition, the MHRA states that all hormonal contraceptives are highly effective and safe, and have important health benefits, including those from avoiding unplanned pregnancy. When used appropriately, the benefits of all combined oral contraceptives far outweigh the risk of VTE. The risk of a venous thrombosis in women who use Yasmin is, as with other combined oral contraceptives, smaller than the risk of VTE associated with pregnancy. As with all oral contraceptives, the Patient Information Leaflet for Yasmin already contains extensive warnings about the risk of VTE. These warnings include the information that in healthy women taking any contraceptive pill, including Yasmin, about 20 to 40 cases of VTE are expected to occur in every 100 000 women each year, depending on the type of progestogen. The corresponding figure for women not using a contraceptive pill is about 5 to 10 cases per 100 000 each year. By comparison, about 60 cases of VTE are expected to occur in every 100 000 pregnancies.

***Reference**:*
Drug Safety Update, MHRA Volume 3, Issue 9, April 2010 (www.mhra.gov.uk).

Irinotecan

Association between UGT1A1 variant alleles and neutropenia

Singapore. Health Sciences Authority (HSA) informed health-care professionals of association between the enzyme uridine diphosphate glucuronosyl transferase 1A1 (UGT1A1) variant alleles and irinotecan-induced severe neutropenia. Irinotecan is used for the treatment of patients with advanced colorectal cancer. Common adverse events associated with irinotecan are diarrhoea, vomiting, nausea and neutropenia. Patients with the variants of the UGT1A1 gene, UGT1A1*28 or UGT1A1*6 are at greater risk of adverse reactions in association with irinotecan.

After reviewing the distribution of UGT1A1 variants in the three major ethnic groups of Singapore (Chinese, Malay and Indian) and the potential impact on the population, the HSA says that the package inserts of all irinotecan-containing products would be updated to include the following cautionary statements: the active metabolite of irinotecan, SN-38, is metabolized predominantly by UGT. It has been reported that patients who are homozygous (UGT1A1*6/*6 or UGT1A1*28/*28) or heterozygous (UGT1A1*6/*28) in allele UGT1A1*6, UGT1A1*28 may be at increased risk for serious adverse reactions (especially neutropenia) caused by reduced glucuronidation of SN-38. Added caution should be exercised when administering in such patients.

Reference:
Adverse Drug Reaction News, April 2010, Vol.12, No.1, HSA (www.hsa.gov.sg).

Naltrexone for extended-release injectable suspension

Medication Guide required for patients

USA. Alkermes and the US FDA notified health-care professionals and patients of an update to the prescribing information of naltrexone for extended-release injectable suspension (Vivitrol) to strengthen language regarding the risk of injection site reactions based on post-marketing reports that had been received prior to June 2009. Naltrexone for extended-release injectable suspension (Vivitrol) is indicated for the treatment of alcohol dependence in patients who are able to abstain from alcohol in an outpatient setting. The US FDA required that a Medication Guide be provided to all patients. Health-care professionals are advised to counsel patients about the risks and benefits of naltrexone for extended-release injectable suspension (Vivitrol) before an initial prescription.

***Reference**:*
Safety Information, US FDA 4 May 2010 (www.fda.gov).

Parenteral amphotericin B

Risk of fatal overdose

UK. The MHRA warned that there is a potential risk of fatal overdose due to confusion between lipid-based and non-lipid-based formulations of parenteral amphotericin B.

Parenteral amphotericin B is available as lipid-based and non-lipid based formulations for the treatment of fungal infections. The appropriate dose and method of administration differ between those formulations of amphotericin B. The Agency emphasizes that they are not interchangeable.

The MHRA says that cases of fatal overdose have resulted when a non-lipid-based formulation of amphotericin B (Fungizone) has been mistakenly administered instead of a lipid-based formulation. Amphotericin B overdoses may result in potentially fatal cardiac or cardiorespiratory arrest. The total daily dose of Fungizone should not exceed 1.5 mg/kg. Health-care professionals are advised to verify the product name and dose before administration, especially if the dose prescribed exceeds 1.5 mg/kg.

***Reference**:*
Drug Safety Update, MHRA Volume 3, Issue 9, April 2010 (www.mhra.gov.uk).

Promethazine hydrochloride injection

Boxed warning added

Canada. Health Canada informed health-care professionals and the public of changes to the prescribing information, including the addition of a boxed warning, for promethazine hydrochloride injection. Injectable promethazine is an antihistamine drug that is used to treat a wide range of conditions, including certain types of allergic reactions, motion sickness, nausea, vomiting and as a sedative. The warning includes the following safety information:

- Promethazine is not to be used in children under the age of two years due to the potentially fatal risk of respiratory depression.
- Caution should be used when administering promethazine in children aged two and up: health care professionals are recommended to use the lowest effective dose, and the use of other drugs that may also slow breathing should be avoided.
- Promethazine is not to be injected subcutaneously due to the risk of serious tissue injury.
- The preferred route of administration for promethazine is deep intramuscular injection. Other routes of injection, particularly into arteries or veins, have been associated with serious tissue injury.
- Regardless of where on the body the drug is injected, promethazine has the potential to occasionally cause chemical irritation and in rare cases severe tissue damage at the site of injection, including cases of gangrene. Patients should immediately report any persistent or worsening pain or burning sensation they feel at the site of injection.

(See WHO Pharmaceuticals Newsletters No. 6, 2009 & No. 1, 2010 and No. 5, 2009 for warnings on the risk of severe tissue injury in New Zealand and the USA, respectively).

***Reference**:*
Advisories, Warnings and Recalls, Health Canada
26 April 2010
(www.hc-sc.gc.ca).

Reports in WHO Global ICSR database, Vigibase:

Promethazine

Injection site reactions (number of events):

	Subcutaneous injection	*Total*
Injection site mass	*1*	*18*
Injection site necrosis	*3*	*36*
Injection site pain	*1*	*123*
Injection site reaction	*5*	*301*
Injection site inflammation	*0*	*89*

Propylthiouracil

Boxed Warning on serious liver injury including liver failure

USA. The US FDA has added a Boxed Warning to the label for propylthiouracil, to include information about reports of severe liver injury and acute liver failure, some of which have been fatal, in adult and paediatric patients using propylthiouracil. Propylthiouracil is used for the treatment of hyperthyroidism. In addition, health-care professionals have been notified of the following information:

- When initiating hyperthyroid treatment, propylthiouracil should be reserved for patients who cannot tolerate methimazole or for patients for whom radioactive iodine therapy or surgery is not appropriate treatment.
- Propylthiouracil may be the treatment of choice when an anti-thyroid drug is needed during and just prior to the first trimester of pregnancy. Fetal abnormalities have been seen with methimazole use during the first trimester of pregnancy.
- Propylthiouracil is not recommended for use in paediatric patients, except in rare instances in which other alternative treatments are not appropriate.

As part of a Risk Evaluation and Mitigation Strategy, the US FDA is also requiring that a *Medication Guide* be given to every patient filling a prescription for propylthiouracil.

The US FDA conducted a search of post-marketing adverse event reports for propylthiouracil submitted to the Agency from 1969 to June 2009, and identified 34 cases of severe liver injury associated with this medicine. Of these, 23 cases were in adult patients and 11 were in paediatric patients. Of the 23 adult cases, 13 deaths and five liver transplants were reported. Among the 11 paediatric cases, two cases resulted in death and seven patients required a liver transplant; one patient died while on the transplant list. The Agency also evaluated post-marketing adverse event reports on methimazole from 1969 to June 2009, and identified five cases of severe liver injury reported with methimazole. All five cases were in adult patients and three resulted in death. Based on these findings and a review of the medical literature, the Agency concluded that use of propylthiouracil is associated with a higher risk for clinically serious or fatal liver injury compared to methimazole in both adult and paediatric patients.

The US FDA also reviewed post-marketing data on birth defects, and found that congenital malformations were reported approximately three times more often with prenatal exposure to methimazole compared to propylthiouracil (29 cases with methimazole and 9 cases with propylthiouracil). The Agency also says that there was a distinct and consistent pattern of congenital malformations associated with the use of methimazole, but not with propylthiouracil. Approximately

90% of the congenital malformations with methimazole were craniofacial malformations (e.g. scalp epidermal aplasia [aplasia cutis], facial dysmorphism and choanal atresia). In the majority of cases, there were multiple malformations which frequently included a combination of craniofacial defects and gastrointestinal atresias or aplasias. These specific birth defects were associated with the use of methimazole during the first trimester of pregnancy. They were not found when the medicine was given later in pregnancy. A consistent pattern of birth defects associated with the use of propylthiouracil was not found. The US FDA concluded that there is no convincing evidence of an association between propylthiouracil use and congenital malformations, even with use during the first trimester.

Reports in WHO Global ICSR database, Vigibase:

Propylthiouracil

Number of reports (SOC liver and biliary system disorders, and additional terms containing liver or hepatic): 269

Most reported reactions (number of events):

SGOT increased	*21*
SGPT increased	*28*
Hepatic failure	*31*
Hepatic function abnormal	*59*
Hepatitis	*83*
Hepatitis cholestatic	*29*
Hepatocellular damage	*25*
Jaundice	*54*

(See WHO Pharmaceuticals Newsletter No. 4, 2009 for the alert regarding an increased risk of hepatotoxicity compared to methimazole in the USA).

Reference:
Safety Information, US FDA 21 April 2010 (www.fda.gov).

Rivastigmine transdermal patch

Serious adverse events related to medication errors / misuse

Canada. Novartis Pharmaceuticals Canada Inc. and Health Canada have informed health-care professionals and the public that serious adverse events including death have occurred following rivastigmine overdose due to medication errors and misuse of rivastigmine transdermal patch (Exelon patch). The Product Monograph is being revised to further emphasize the following safety information:

- Health-care providers should inform patients and caregivers on the proper use of rivastigmine patch prior to initiating therapy, and advise them to strictly follow instructions on patch usage;
- Only one transdermal patch should be applied per day to healthy skin on one of the recommended locations: the upper or lower back, or upper arm or chest;
- The previous day's patch must be removed before applying a new patch to a different skin location after 24 hours of use;
- The patch should not be cut into pieces;
- In case of overdose, all Exelon transdermal patches should be immediately removed and the patient should be evaluated by a physician.

According to the company, as of 31 July 2009, a total of 129 cases of medication errors and misuse, including 2 cases with fatal outcomes, have been reported with rivastigmine transdermal patch (Exelon patch) worldwide. The most frequently reported causes of overdose are failure to remove the patch before applying a new patch and application of more than one patch at the same time. The typical symptoms reported in association with overdose include nausea, vomiting, diarrhoea, hypertension, hallucinations, salivation, sweating, respiratory depression and convulsions. Bradycardia and/or syncope may also occur.

Reference:
Advisories, Warnings and Recalls, Health Canada 5 May 2010 (www.hc-sc.gc.ca).

Saquinavir mesilate

Association with QT and PR interval prolongation

Canada. Health-care professionals were warned about prolongations of QT and PR intervals associated with saquinavir mesylate (Invirase), based on the findings of an electrocardiogram study with saquinavir mesylate and ritonavir in healthy volunteers. Saquinavir mesylate in combination with ritonavir and other antiretrovirals is indicated for the treatment of HIV-1 infected adult patients. The letter sent to health-care professionals states that dose-dependent prolongations of QT and PR intervals have been observed in healthy volunteers receiving ritonavir-boosted saquinavir mesylate. The company and Health Canada advise that ritonavir-boosted saquinavir mesylate not be used in patients already taking medications known to cause QT interval prolongation, such as Class IA (e.g. quinidine, procainamide) or Class III (e.g.

amiodarone, sotalol) antiarrhythmic drugs, or in patients with a history of QT interval prolongation. Caution should be taken when administering ritonavir-boosted saquinavir mesylate with any medication which can significantly increase either the QT or PR interval. Caution is also warranted when administering ritonavir-boosted saquinavir mesylate to patients with a known history of QT prolongation or medical conditions predisposing to QT prolongation (e.g. electrolyte disturbances) and/or patients with pre-existing conduction system disease (e.g. first-degree AV block or second- or third degree AV block). The Canadian Product Monograph has been updated accordingly.

(See WHO Pharmaceuticals Newsletter No. 2, 2010 for ongoing safety review of clinical trial data in the USA).

Reference:
Advisories, Warnings and Recalls, Health Canada 20 April 2010 (www.hc-sc.gc.ca).

Simvastatin

Increased risk of myopathy at high dose

UK. The MHRA warns that there is an increased risk of myopathy associated with high-dose (80 mg) simvastatin. It is advised that the 80-mg dose should be considered only in patients with severe hypercholesterolaemia and high risk of cardiovascular complications who have not achieved their treatment goals on lower doses, when the benefits are expected to outweigh the potential risks. In the UK, the simvastatin (Zocor) product information has been updated to include warnings about increased risk of myopathy in patients receiving the highest licensed dose (80 mg).

This update follows a review of the Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine (SEARCH), which is a multicentre, double-blind, active-treatment, factorial-design study conducted at 88 sites in the UK. The MHRA explains that SEARCH evaluated the effect of treatment with simvastatin (Zocor) 80 mg versus 20 mg on major vascular events (MVEs, defined as fatal coronary events, non-fatal myocardial infarction, coronary revascularisation procedure, non-fatal or fatal stroke, or peripheral revascularisation procedure) in 12 064 patients with a history of myocardial infarction, over a median follow-up of 6 to 7 years. The results showed that treatment with simvastatin 80 mg did not provide any significant benefits over simvastatin 20 mg. The incidence of MVEs was similar for those two groups (80 mg versus 20 mg). There was no evidence of increased total or cause-specific mortality, vascular mortality, non-vascular mortality, or higher risk of cancer or haemorrhagic stroke with the high dose of simvastatin. However, myopathy occurred in 52 patients (0.9%) randomly assigned simvastatin 80 mg compared with one patient (0.02%) randomly assigned simvastatin 20 mg. An estimated 11 patients in the simvastatin 80-mg group developed rhabdomyolysis compared with none in the simvastatin 20-mg group.

Reference:
Drug Safety Update, MHRA, Volume 3, Issue 10, May 2010 (www.mhra.gov.uk).

Zoledronic acid

Risk of renal impairment and renal failure

UK. The MHRA warns that zoledronic acid is associated with reports of renal impairment and renal failure, especially in patients with pre-existing renal dysfunction or other risk factors. Zoledronic acid 5 mg for infusion (Aclasta) is used for the once-yearly treatment of osteoporosis in patients at increased risk of fracture, and as a single dose for the treatment of Paget's disease of the bone. Zoledronic acid 4 mg for infusion (Zometa) is given every 3 to 4 weeks for the reduction of bone damage in advanced malignancies involving bone, and as a single dose for tumour-induced hypercalcaemia. According to the Agency, there have been 139 worldwide suspected reports (14 fatal) of renal impairment or renal failure up to 14 August 2009, and six UK suspected reports (one fatal) of renal impairment or renal failure up to 5 March 2010, following the administration of zoledronic acid (Aclasta). The majority of cases were associated with the first dose, and generally occurred in patients with pre-existing renal dysfunction or other risk factors, including: advanced age; use of concomitant nephrotoxic drugs or diuretic therapy; or dehydration. Renal failure requiring dialysis or resulting in death has occurred in some at-risk patients. Warnings in the product information for zoledronic acid (Aclasta) are being strengthened following reports of renal failure or renal impairment with its use.

Health-care professionals are advised to take precautions including the following in order to minimize the risk of renal

adverse reactions with zoledronic acid:

- Renal function should be measured before each infusion of zoledronic acid.
- Patients, especially elderly patients and those receiving diuretic therapy, should be appropriately hydrated before administration of zoledronic acid.
- Monitoring of renal function after zoledronic acid infusion should be considered, particularly in at-risk patients such as: those with pre-existing renal dysfunction; those of advanced age; those using concomitant nephrotoxic drugs or diuretic therapy; or those who are dehydrated.
- Zoledronic acid should be used with caution when used concomitantly with medicines that could affect renal function.
- Zoledronic acid (Zometa) for cancer treatment is not recommended for use in patients with creatinine clearance <30 mL/min, and should only be considered for the treatment of hypercalcaemia in cancer patients with severe renal impairment after evaluating the risk and benefits of treatment.

Reports in WHO Global ICSR database, Vigibase:

Zoledronic acid

High Level term Renal function abnormal	
Albuminuria	*26*
Azotaemia	*419*
Creatinin clearance decreased	*51*
Renal failure acute	*207*
Renal failure chronic	*197*
Renal function abnormal	*143*

***Reference**:*
Drug Safety Update, MHRA, Volume 3, Issue 9, April 2010 (www.mhra.gov.uk).

Antidepressants

Risk of fractures

UK. The MHRA advised health-care professionals that a review of epidemiological studies, mainly in patients age 50 years or older, shows an increased risk of bone fractures in patients receiving selective serotonin reuptake inhibitors (SSRIs) and tricyclic antidepressants (TCAs). The mechanism leading to this increased risk is unclear. The Agency states that the review concluded that product information should be updated with a statement on epidemiological findings of an increased risk of bone fractures with TCAs and SSRIs. From the available data, no definite conclusions could be drawn regarding a dose-response relation, time relation or the underlying mechanism.

Reference:
Drug Safety Update, MHRA, Volume 3, Issue 10, May 2010 (www.mhra.gov.uk).

Carbapenems

Concomitant use with valproic acid not recommended

UK. The MHRA warns that concomitant use of carbapenems and valproic acid/sodium valproate is not recommended, because a clinically significant interaction between carbapenems and valproic acid results in reduced valproate plasma concentrations with potential for inadequate seizure control. Health-care professionals are advised to consider alternative antibacterial therapy. Carbapenems are a class of beta-lactam antibiotics with broad-spectrum antibacterial activity. They are indicated for the treatment of the following infections when caused by susceptible bacteria: nosocomial pneumonia; complicated intra-abdominal infections; and complicated urinary tract infections. Valproic acid/sodium valproate is an anticonvulsant used for the treatment of generalized, partial or other epilepsy.

The MHRA explains that an interaction between carbapenems and valproic acid has been described in a number of case reports and one identified study. A more recent unpublished pharmacokinetic study of 24 healthy human volunteers found that concomitant administration of valproic acid and doripenem resulted in a rapid and substantial fall in plasma valproate levels. Given the large magnitude and rapid time course of this interaction, monitoring of sodium valproate levels or making dose adjustments are unlikely to manage this interaction. A Europe-wide class review of data for the remaining carbapenems found that decreased valproic acid levels have also been reported when co-administered with other carbapenems, with 60 to 100% decreases in valproic acid levels being observed within about two days. This interaction is therefore likely to be a class effect.

Reference:
Drug Safety Update, MHRA, Volume 3, Issue 10, May 2010 (www.mhra.gov.uk).

Clopidogrel and proton-pump inhibitors

Updated advice on possible interactions

UK. The MHRA updated the advice on concomitant use of clopidogrel and proton-pump inhibitors (PPIs). Previously, it was advised that concomitant use of any PPIs with clopidogrel should be avoided unless considered essential. Since then, new evidence has become available which casts some doubt on the clinical relevance of possible interactions between clopidogrel and PPIs. In light of the most recent evidence, the MHRA states that the previous advice is no longer considered necessary for PPIs other than omeprazole and esomeprazole. With regard to omeprazole and esomeprazole, as a precaution, concomitant use of clopidogrel with omeprazole or esomeprazole should be discouraged. The Agency explains that pharmacokinetic, pharmacodynamic and some clinical outcome data suggest a significant interaction for omeprazole, and there is also some evidence in relation to esomeprazole. Information for prescribers and patients will be updated with the latest advice.

Health-care professionals are also advised:

- to consider PPIs other than omeprazole or esomeprazole in patients who are taking clopidogrel. Other gastrointestinal therapy such as H2 blockers (except cimetidine) or antacids may be more suitable in some patients.
- to discourage concomitant use of other known CYP2C19-inhibiting medicines with clopidogrel because these are expected to have a similar effect to omeprazole

and esomeprazole (CYP2C19 inhibitors include fluvoxamine, fluoxetine, moclobemide, voriconazole, fluconazole, ticlopidine, ciprofloxacin, cimetidine, carbamazepine, oxcarbazepine and chloramphenicol).

(See WHO Pharmaceuticals Newsletter No. 2, 2010 for updates on warning about interaction between clopidogrel and proton pump inhibitors in Europe and New Zealand).

Reference:
Drug Safety Update, MHRA, Volume 3, Issue 9, April 2010 (www.mhra.gov.uk).

Eltrombopag

Portal venous system thromboses in study of patients with chronic liver disease

USA. GlaxoSmithKline and the US FDA notified health-care professionals of a new safety finding in patients with thrombocytopenia due to chronic liver disease treated with eltrombopag. Eltrombopag (Promacta) is a thrombopoietin receptor agonist approved for the treatment of thrombocytopenia in adult patients with chronic immune (idiopathic) thrombocytopenic purpura. In a study of thrombocytopenic patients with chronic liver disease of diverse etiology, patients were treated with eltrombopag 75mg or matching placebo for 14 days prior to undergoing an elective invasive procedure. The study was terminated following the identification of an imbalance of thrombosis of the portal venous system in the patients treated with eltrombopag versus matching placebo. Six patients (4%) in the eltrombopag group and one (1%) in the placebo group experienced a thrombotic event of the portal venous system. Five of the six patients treated with eltrombopag experienced the portal venous thrombosis at platelet counts above 200,000/µl.
The following advice for health-care professionals was issued.

- Eltrombopag (Promacta) is indicated for the treatment of thrombocytopenia in adult patients with chronic immune (idiopathic) thrombocytopenic purpura and is not indicated for the treatment of thrombocytopenia in patients with chronic liver disease.
- Treatment with eltrombopag (Promacta) should be aimed at increasing the platelet count to a level that reduces the risk of bleeding; eltrombopag (Promacta) should not be used in an attempt to normalize the platelet count.
- Use caution when administering eltrombopag (Promacta) to patients with known risk factors for thromboembolism.
- Exercise caution when administering eltrombopag (Promacta) to patients with hepatic disease. Use a lower starting dose (25mg once daily) of eltrombopag (Promacta) in patients with moderate to severe hepatic disease and monitor closely.

***Reference**:*
Safety Information, US FDA 12 May 2010 (www.fda.gov).

Entacapone / carbidopa / levodopa

Possible increased risk for prostate cancer

USA. The US FDA notified health-care professionals and patients that it is evaluating data from a long-term clinical trial called Stalevo Reduction in Dyskinesia Evaluation - Parkinson's Disease (STRIDE-PD), which may suggest that patients taking Stalevo may be at an increased risk for developing prostate cancer. Stalevo contains a combination of the active ingredients entacapone, carbidopa and levodopa, and is used to treat Parkinson's disease. The STRIDE-PD trial evaluated the time to onset of dyskinesia in patients with Parkinson's disease taking Stalevo compared to those taking only carbidopa/levodopa (Sinemet). The Agency explains that a greater number of patients taking Stalevo were observed to have prostate cancer compared to those taking carbidopa/levodopa. Previous controlled clinical trials of shorter duration evaluating entacapone/carbidopa/levodopa (Stalevo) in Parkinson's disease have not found an increased risk of prostate cancer, and prostate cancer is most commonly diagnosed in men who are of the same age as men included in the STRIDE-PD trial.

At this time, the review by the US FDA is ongoing and the Agency has not concluded that Stalevo increases the risk of developing prostate cancer. The US FDA advises that health-care professionals should be aware of this possible risk and follow the recommendations in the drug label when prescribing entacapone/carbidopa/levodopa (Stalevo) and entacapone (Comtan), which is also used to treat Parkinson's disease.

Reference:
Safety Information, US FDA 31 March 2010 (www.fda.gov).

Gonadotropin-Releasing Hormone Agonists

Ongoing review on the possible increased risk of diabetes and cardiovascular diseases

USA. Health-care professionals and patients are informed that the US FDA is evaluating whether Gonadotropin-Releasing Hormone (GnRH) Agonists may increase the risk of diabetes and certain cardiovascular diseases (heart attack, sudden cardiac death, stroke) in men receiving these medicines for the treatment of prostate cancer. GnRH agonists suppress the production of testosterone, which is involved in the growth of prostate cancer, and are used to treat prostate cancer. This therapy is known as Androgen Deprivation Therapy or ADT.

According to the Drug Safety Communication, the US FDA is reviewing data from published studies comparing outcomes in patients undergoing ADT to treat prostate cancer versus patients not undergoing this treatment. Most of these studies reported small, statistically significant increased risks of diabetes and/or cardiovascular events in patients undergoing ADT. However, there are several study design limitations that make a cause-and-effect relationship difficult to confirm.

The review is ongoing and the Agency has not made any conclusions whether GnRH agonists increase the risk of diabetes and cardiovascular diseases in patients receiving these medications for prostate cancer.

At this time, the US FDA advises that health-care professionals and patients should be aware of these potential safety issues and carefully weigh the benefits and risks of GnRH agonists when determining treatment choices. The Agency recommends that patients receiving GnRH agonists should be monitored for development of diabetes and cardiovascular disease. It is also recommended that health-care professionals should manage cardiovascular risk factors for patients, such as smoking and increases in blood pressure, cholesterol, blood sugar, and weight.

The Agency also notes that some GnRH agonists are used in women and in children for other indications than those above. There are no known comparable studies that have evaluated the risk of diabetes and heart disease in women and children taking GnRH agonists.

Reference:
Safety Information, US FDA 3 May 2010 (www.fda.gov).

H1N1 pandemic vaccines and antiviral

Reports of suspected adverse reactions

Europe. The European Medicines Agency regularly issues pandemic pharmacovigilance updates that include a summary of the adverse drug reactions reported after the use of centrally authorized pandemic vaccines (Arepanrix, Celvapan, Focetria and Pandemrix) and the antiviral (oseltamivir (Tamiflu)).

According to the eighteenth pharmacovigilance update, as of 9 May 2010, a total of 14,554 case reports had been received from the European Economic Area by EudraVigilance since the authorization of the centrally authorized vaccines (Arepanrix, Celvapan, Focetria and Pandemrix) in the EEA. (Arepanrix is not marketed in the EEA). With regard to oseltamivir (Tamiflu), from 1 April 2009 to 9 May 2010, a total of 1101 reports worldwide were received by EudraVigilance.

The vast majority of the adverse reactions that had been reported as of 9 May 2010 are considered to be non-serious. The benefit-risk balance of the centrally authorized pandemic vaccines and antivirals for the current H1N1 influenza pandemic continues to be positive.
Details of the reported reactions are available on the EMA website.

Reference*:*
Pandemic pharmacovigilance update, EMA (www.emea.europa.eu).

Leflunomide

Peripheral neuropathy

Canada. In Canada, cases of peripheral neuropathy have been reported in association with leflunomide. Leflunomide is a disease-modifying antirheumatic drug (DMARD) indicated for use in adults with active rheumatoid arthritis. Neuropathy has been reported in association with several DMARDs, including sulfasalazine, chloroquine and penicillamine.

According to the Canadian Adverse Reaction Newsletter, from the date of marketing (in 2000) to 31 October 2009, Health Canada received 26 adverse reaction reports of peripheral neuropathy symptoms suspected of being associated with the use of leflunomide. Peripheral neuropathy was specified in 9 of the reports; the remaining 17

reports described signs and symptoms of peripheral neuropathy such as paraesthesia, hypoesthesia or burning sensation of the skin. Of the 26 cases, 23 were reported by health care professionals and 22 were reported as serious. There were 17 women and 7 men (sex not reported in 2 cases). The greater number of women could be explained by the fact that rheumatoid arthritis is three times more likely in women than in men. Some confounding factors reported in the cases included concomitant diseases (e.g., rheumatoid arthritis, diabetes) and concomitant drugs (e.g., methotrexate, hydroxychloroquine). Electrophysiologic studies had been conducted in 4 of the 9 cases reported as peripheral neuropathy, and the results were positive in 3 cases. The duration of leflunomide therapy in these 9 cases varied from 2 months to 2 years. In 9 of the 26 cases, the reaction abated after stopping the drug.

During the last seven years, additional data regarding the suspected association between peripheral neuropathy and leflunomide have emerged in the medical literature. Patients had paraesthesia or weakness, or both, in the upper or lower extremities, or both. In a few cases, the symptoms were severe or debilitating. The incidence of peripheral neuropathy has ranged from 1.4% to 10% in open studies to assess leflunomide neurotoxicity. In these studies, the proportion of patients for whom this adverse reaction improved after discontinuation of the drug or reduction of the dosage ranged from 37% to 100%.

Reference:
Canadian Adverse Reaction Newsletter Volume 20, Issue 2, Health Canada, April 2010 (www.hc-sc.gc.ca).

Natalizumab

Update on the risk of progressive multifocal leukoencephalopathy

Canada. Health-care professionals have been advised that the risk of developing progressive multifocal leukoencephalopathy (PML) increases with increasing duration of natalizumab (TYSABRI) treatment, and that after 24 infusions, the risks and benefits of continuing natalizumab therapy should be re-discussed with the patient. The Canadian Product Monograph for natalizumab has been updated to include this additional safety information. Natalizumab is a humanized monoclonal antibody that is authorized as monotherapy for the treatment of patients with relapsing-remitting multiple sclerosis (MS). All patients who are prescribed natalizumab are to be enrolled in the Tysabri Care Program™ (TCP), which is a registry of patients.

According to the Dear Health Care Professional letter, in patients treated with natalizumab for up to 3 years the incidence of PML increases with longer treatment duration. As of 31 December 2009, approximately 64 600 patients were receiving natalizumab worldwide. As of 6 April 2010, 46 confirmed cases of PML had been reported. In patients treated for greater than 24 months in the post-marketing setting, the incidence rate of PML is 1.59 per 1000 (95% CI 1.11 - 2.21), compared to a rate of approximately 1 per 1000 in clinical trials. There is limited experience beyond 3 years of treatment, and therefore the risk of PML in these patients cannot be reliably estimated.

(See WHO Pharmaceuticals Newsletters No.2, 2002 for updates on the risk of PML and IRIS in the UK and the USA as well as No.1, 2010 for recommendations of new measures to minimize the risk of PML in Europe).

Reference:
Advisories, Warnings and Recalls, Health Canada
17 May 2010
(www.hc-sc.gc.ca).

Oral tacrolimus

Measures to reduce risk of medication errors

UK. The MHRA notified the measures to reduce risk of medication errors in relation to oral tacrolimus products. Tacrolimus is an immunosuppressant with a narrow therapeutic index, which may be given orally to prevent or treat organ transplant rejection. There are three different formulations of tacrolimus and they are not interchangeable. The Agency warns that switching between the different formulations of oral tacrolimus requires careful therapeutic monitoring and the close supervision of a transplant specialist.

- Prograf and Adoport are immediate release capsule formulations taken twice daily. Generic immediate-release tacrolimus capsules are bioequivalent with Prograf and may be interchanged.
- Advagraf is a prolonged release capsule formulation taken once daily.
- Modigraf is a granule formulation for oral suspension taken twice daily

but is not bioequivalent with Prograf or Advagraf.

According to the MHRA, by the end of February 2010, it had received 12 case reports involving prescribing/dispensing errors in association with oral tacrolimus. These included: four cases of acute rejection reaction; three cases of increased drug levels; and two cases of increased creatinine.

In order to minimize the risk of future medication errors and unintended switching between the different formulations, the Commission on Human Medicines and the MHRA recommend that prescribers should either: provide full information, stating on the prescription the drug, the exact pharmaceutical form (capsules or granules; immediate-release or prolonged-release), the strength, and the posology (dose and dose frequency); or prescribe by brand name and include the strength and posology (dose and dose frequency). Pharmacists should always dispense the exact pharmaceutical form and strength or brand and strength of oral tacrolimus that has been prescribed, and should contact the prescriber if the prescriber's intention is not clear, to ensure that the appropriate medicine is dispensed.

Reference:
Drug Safety Update, MHRA, Volume 3, Issue 10, May 2010 (www.mhra.gov.uk).

SSRIs and SNRIs

Risk of persistent pulmonary hypertension in the newborn

UK. The MHRA advised that epidemiological data suggest that the use of selective serotonin reuptake inhibitors (SSRIs), which are antidepressant medicines, in pregnancy, particularly in the later stages, may increase the risk of persistent pulmonary hypertension in the newborn (PPHN). The observed risk was approximately five cases per 1000 pregnancies whereas the background rate in the general population is one to two cases of PPHN per 1000 pregnancies. PPHN presents as severe hypoxaemia due to pulmonary artery hypertension. The Agency says that although there is no evidence for the association of PPHN to noradrenaline reuptake inhibitors (SNRIs) treatment, this potential risk cannot be ruled out taking into account the related mechanisms of action. Health-care professionals are encouraged to enquire about the use of SSRIs and SNRIs, particularly in women in the later stages of pregnancy. Close observation of neonates exposed to SSRIs or SNRIs for signs of PPHN is recommended after birth.

Reference:
Drug Safety Update, MHRA, Volume 3, Issue 10, May 2010 (www.mhra.gov.uk).

Collaborative participation of inspectors from national Medicines Regulatory Authorities (MRAs) in inspections coordinated by the WHO Prequalification of Medicines Programme

Deusdedit K. Mubangizi, Prequalification of Medicines Programme, WHO

Background:

The basic strategy of the WHO Prequalification of medicines Programme (WHO-PQM) is to cooperate with national Medicines Regulatory Agencies (MRAs) to comprehensively evaluate the quality, safety and efficacy of medicinal products, based on information submitted by the manufacturers, and inspection of the manufacturing and clinical sites. The programme currently focuses on products for the treatment of HIV/AIDS, Malaria, Tuberculosis, Reproductive Health and selected individual products for other diseases such as oseltamivir (used in the management of influenza) and zinc sulphate (used in the management of acute diarrhoea in children).

Increasingly, collaboration with and training of inspectorate staff from MRAs for sustainable evaluation and monitoring of the quality of medicines used in their countries has become one of the key strategies of the programme. Normally, each PQ inspection is conducted by a WHO inspector, a co-inspector from one of the Pharmaceutical Inspection Cooperation Scheme (PICS) member countries, an observer from the MRA of the host country and, in some cases, an observer from MRA of a potential recipient country.

These collaborative and capacity building activities have also been found to be effective catalysts for harmonization of medicines regulation in countries not being members of the International Conference of Harmonization (ICH).

What is the collaborative procedure?

Encouraged by the feedback from these activities, WHO-PQ has embarked on strengthening the capacity building strategies. This strategy includes a more targeted involvement of inspectors from MRAs of developing countries and other interested member states in inspections organized by the WHO-PQ (including joint inspections) and better sharing of inspections related information. This has the following objectives:

- Training of inspectors from MRAs of developing countries and other interested member states.
- Facilitating use of WHO-PQ inspection results by MRAs for information and decision making.
- Harmonization of inspection practices through joint inspections and sharing of outcomes.
- Sharing the workload and avoiding duplicative inspections

Nominated inspectors from MRAs of developing countries and other interested Member States will be invited to participate in WHO-PQ organized inspections and in turn, the MRAs will be given access, though a secured website, to outcomes of these inspections.

National MRAs (NMRAs) will share their inspection plans with participating countries. WHO-PQ shall allocate the nominated inspectors to the scheduled inspections considering their qualifications and experience. For more details, please see the web site at www.who.int/prequal.

Why is WHO-PQM starting this procedure?

The collaborative procedure is in line with the mission and strategy of the WHO-PQM and also answers the request of Member States;

Mission
In close cooperation with national regulatory agencies and partner organizations, the WHO-PQM aims to make quality, priority medicines available for the benefit of those in need.

Strategy
- Apply unified standards of acceptable quality, safety and efficacy.
- Comprehensively evaluate the quality, safety and efficacy of medicinal products, based on information submitted by the manufacturers, and inspection of the corresponding manufacturing and clinical sites.
- Prequalify quality control laboratories of pharmaceuticals.
- Build the capacity of staff from national regulatory authorities, quality control laboratories, and from manufacturers or other private companies, to ensure medicines quality.

This nature of collaboration and capacity building has also been requested by Member States through their NMRAs as can be seen from the resolutions of the thirteenth ICDRA, 2008. (http://www.who.int/medicines/areas/quality_safety/regulation_legislation/icdra/Recommendations_13ICDRA.pdf).

Theme: Building mutual trust as a key to access
Recommendation from this session at the ICDRA was as follows:
WHO should, in partnership with well-resourced regulatory authorities, establish formal mechanisms for the exchange and use of regulatory information among all authorities to strengthen capacity and to maximize efficiencies

Theme: Regulatory systems in a changing environment
The Recommendation related to this session was that
Member States should:
- Facilitate and speed up global regulatory cooperation.
- Support and stimulate their regulatory authorities to work with regional and global partners.

WHO should:
- Continue to support and create new activities that stimulate cooperation and build trust among regulatory agencies.

Who can participate?

Any MRA of a WHO Member State can express an interest in collaborating with the WHO PQM programme in the inspection activities.

MRAs of developing countries and/or of countries participating in harmonization initiatives of their regulatory activities are particularly encouraged to participate as part of their capacity building.

Participation in the prequalification procedure is voluntary. This invitation is not limited to MRA from a specific region. However, WHO reserves the right to prioritize the collaboration with:

- MRAs which have an urgent need and commitment for capacity building, and
- MRAs in regions pursuing harmonization of their regulatory activities.
- MRAs (belonging to PIC/S) providing WHO-PQ substantial support in terms of making their inspectors available for WHO as co-inspectors.

How can a MRA participate in the collaborative procedure?

Any MRA wanting to participate in the collaborative procedure should provide WHO-PQM with:

1. A letter expressing interest in participating in the WHO Collaborative Procedure for inspections.
2. Information on the MRA, compiled in the prescribed format and giving sufficient information on:
   - The head of the MRA.
   - The focal person for inspections.
   - Names, qualifications and experience of MRA inspectors.

All of the above-mentioned information should be submitted in English. Submissions that are not made in English must be accompanied by a certified English translation.

Details about the application can be found at:
http://apps.who.int/prequal/info_general/documents/inspection/NMRAs/GUIDANCE_WHO-PQM_NMRAs_CollaborativeProcedure.pdf

What guidelines and standards shall be used?

WHO norms and standards for Good Manufacturing Practices (GMP), Good Clinical Practice (GCP) and Good Laboratory Practice (GLP) shall be the basis for inspection together with other relevant international guidelines (such as those from ICH). WHO will coordinate these inspections and shall have the responsibility for the inspection under the collaborative procedure.

Will participating MRAs be bound by the conclusion of the inspection outcome?

The conclusion on the outcome of the inspection is the prerogative of the national inspectorate and it is not mandatory for another inspectorate to accept the outcome. Although this is not expected, a participating MRA may reach a conclusion on the outcome of an inspection different from that reached by WHO, as a result of risk analysis under the national situation.

Nevertheless, it is hoped that the outcomes of the collaborative inspection shall be utilized by concerned authorities for building regulatory capacity, saving of resources, acceleration of national registrations for medicines and complementing their national quality assurance measures.

What about confidentiality and conflict of interest?

Appointed experts (inspectors and observers) are bound by confidentiality agreements and have to treat all information submitted and observed during site inspections as strictly confidential and proprietary to WHO or parties collaborating with WHO in accordance with the terms contained in an agreement.

Where should the Expression of Interest be sent?

The submissions containing the covering letter and the completed 'Expression of Interest' form should be sent to:

Dr Adriaan van Zyl
Prequalification of Medicines Programme
World Health Organization
HSS/EMP/QSM Room 625
20 Avenue Appia
1211 Geneva 27
Switzerland

Expected outcomes

It is hoped that this collaborative procedure will have many benefits. It will lead to capacity building of inspectorates of NMRAs of developing countries, and other interested member states, through "hands-on" training in inspection, practical interpretation and application of international norms and standards. Participating inspectors are likely to develop similar skill levels, similar approaches to inspection and practical experience in multi-agency collaboration which will then facilitate harmonization of regulatory practices. This will, in turn, lead to faster access to good quality essential medicines, including those prequalified by WHO.

The approach and skills could be used to facilitate harmonized inspections among regional NMRAs even in product categories outside the focus of WHO-PQM.

Workshop on Pharmacovigilance Systems in West Africa

A four-day workshop on pharmacovigilance systems for countries belonging to the Economic Community of West African States (ECOWAS) took place in Accra, Ghana, 10 - 13 May 2010. ECOWAS consists of fifteen West African countries and West Africa Health Organization (WAHO) is linked to this community.

The overall objective of the meeting was to ensure that countries develop simple and practical country plans that will enable them to either establish PV systems in their countries or strengthen existing systems. Participants from 14 ECOWAS countries took part in the workshop and discussed issues relating to the establishment, strengthening and proper operations of pharmacovigilance systems in each ECOWAS country.

Participants and facilitators in the workshop

The workshop was sponsored and organized by WAHO and was hosted by the WHO Collaborating Centre (WHO CC) for Advocacy and Training in Pharmacovigilance located at the University of Ghana Medical School. Representatives from WHO-AFRO (Malaria Programme), the WHO Ghana country office, the Pharmacovigilance Programme at WHO-HQ and the WHO CC for International Drug Monitoring (the Uppsala Monitoring Centre) were invited to attend and facilitate.

The Deputy-Minister of Health of Ghana, Mr Rojo Mettle-Nunoo pledged government support to assist WAHO in this endeavor and urged all health ministers in the sub-region to place a high premium on patient safety and pharmacovigilance. He called for special efforts to tackle the issue of fake, counterfeit and substandard medicines.

Pharmacovigilance, the science and activities relating to the assessment, detection and prevention of adverse drug effects and any other drug related problems is a medical activity as yet poorly established within the health systems of West Africa. Pharmacovigilance is essential to prevent drug-related problems and to ensure rational use of medicines. The Pharmacovigilance team in World Health Organization (WHO) supports the development of responsive pharmacovigilance systems, particularly in

countries where access to medicines is improving but where there is little or no capacity to monitor the safety of those medicines.

Currently, only five out of the 15 countries in ECOWAS have a national pharmacovigilance system and collaborate as full members of the World Health Organization Programme for International Drug Monitoring (hereafter, the WHO Programme). Four countries are Associate Members, indicating that they have started a system but do not yet have the technical competence to become full members of the WHO Programme. The presence of functional pharmacovigilance systems in the region will lead to the early identification of any drug-related problems. Effective communication of such drug safety signals could help prevent medicine-associated harm in the more than 250 million inhabitants in West Africa.

The current workshop aimed to examine pharmacovigilance systems in West Africa and to chart a way forward. Participants discussed issues related to the establishment, strengthening and proper operations of pharmacovigilance systems. The overall objective of the meeting was to ensure that countries develop simple and practical country plans that will enable them to either establish pharmacovigilance systems in their countries or strengthen existing systems.

Each country undertook an assessment of the strengths and weaknesses of its national pharmacovigilance system and worked with the facilitators to develop strategies to bridge any identified gaps. All countries called for support for expansion of existing programmes, and development of programmes to educate and motivate reporters as well as providing feedback to all stakeholders in the system. Whilst optimistic that a viable pharmacovigilance system can be established in West Africa, participants were also pragmatic about the challenges of pharmacovigilance in Africa and called for realistic plans to build sustainable programmes.

At the end of the intensive, exciting and very profitable four days, the following recommendations were made by participants for consideration by WAHO, Health Ministers, potential donor agencies and all stakeholders in medicine safety and the overall medicines supply chain:

1. Robust, sustainable and responsive pharmacovigilance systems should be developed and supported in all countries in West Africa.

2. National Medicines Regulatory Authorities should play a key and central role in any pharmacovigilance efforts.

3. The pharmacovigilance systems developed should not be disease or medicine specific, but should cut across health issues of the whole country and should be viewed as a health systems issue.

4. ECOWAS countries should include a budget line for pharmacovigilance as part of their respective health budgets.

5. Training in IT and communication in pharmacovigilance will ensure that not only will countries generate adverse drug reaction data, but will also manage their own country data in order to make health policy decisions at country level and also share data quickly with other countries in the sub-region.

6. Documentation and literature available from the WHO/UMC should be available in multiple languages, specifically; English, French and Portuguese in order that all countries can easily access this without the need for translation.

7. Countries that have not achieved full membership status of the WHO Programme for International Drug Monitoring should be encouraged and supported to do so.

8. A course in pharmacovigilance should be included in the curriculum of health-care studies in various countries.

9. The WHO Collaborating Centre (WHO-CC) for Advocacy and Training in Pharmacovigilance in Accra should be supported and its capacity extended so that it can act as a Reference Centre for pharmacovigilance in Africa.

10. The WHO-CC in Accra in collaboration with the WHO (AFRO and HQ) and UMC should provide technical support in the region.

11. Participants should plan on high-level advocacy with their national authorities to ensure that interest in and support for pharmacovigilance is maintained and sustained.

12. WAHO should continue to play a coordinating and mobilizing role for pharmacovigilance in Africa, including providing support for the mobilization of financial resources for pharmacovigilance.

13. National Medicine Regulators should be part of decisions related to, or resulting from pharmacovigilance at country level.

14. Yearly meetings should be planned to look at specific pharmacovigilance topics pertaining to the West African Region and biannual meetings should be organized to discuss general issues.

15. Pharmacovigilance activities in West Africa should be harmonized and WAHO should consider supporting cross-country research in pharmacovigilance and pharmacoepidemiology.

16. Communication is a key part of pharmacovigilance and training should be provided in all aspects of communication.

17. Pharmacovigilance centres in West Africa should be supported to develop the ability to manage medicinal-products related crisis. They should be provided training and support in Crisis Management and assisted to develop their Crisis Management Plans.