WHO PHARMACEUTICALS NEWSLETTER

World Health Organization

prepared in collaboration with the
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This is a double edition, that combines volumes No. 6, 2009 and No. 1, 2010. Some of the information might therefore be a bit outdated but we wish to present them anyhow, for those of you who do not have ready access to this information from other sources. Under 'Feature' we include an article on the WHO programme for the prequalification of quality control laboratories; and the recommendations from the thirty-second meeting of representatives participating in the WHO Programme for International Drug Monitoring.

We wish you all a very good year in 2010. And thank you for your interest in the newsletter

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

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

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Benfluorex

Withdrawal recommended

Europe. The European Medicines Agency (EMEA) has recommended the withdrawal of all medicines containing benfluorex in the European Union, because their risks, particularly the risk of heart valve disease, are greater than their benefits. Benfluorex is approved for use in overweight patients with diabetes, combined with an appropriate diet.

This recommendation follows a review by the EMEA's Committee for Medicinal Products for Human Use (CHMP) on the safety and efficacy of benfluorex. The CHMP considered that the data indicate a risk of heart valve diseases associated with the use of benfluorex, and that the efficacy of benfluorex in the treatment of diabetes is limited. Therefore, the Committee concluded that the benefits of benfluorex no longer outweigh its risks, and recommended the revocation of all marketing authorisations for medicines containing benfluorex in the European Union.

The EMEA advises that doctors should stop prescribing benfluorex and consider alternative treatments. For patients currently treated with benfluorex, the Agency recommends making an appointment with their doctor at a convenient time, to change their prescription. In addition, patients who have taken benfluorex in the past are advised to mention this to their doctor so that they can be checked for the signs and symptoms of heart valve disease, because heart valve disease can develop some years after treatment.

Reports in WHO Global ICSR database, Vigibase

Benfluorex

Reported reactions (number of events):
Aortic valve incompetence: 2
Heart valve disorders: 6
Mitral insufficiency: 8

Reference:
Press Release, Questions and Answers, EMEA
18 December 2009
(www.emea.europa.eu).

Ceftriaxone

Incompatibility with calcium-containing solutions

Canada (1). Health Canada has issued a Notice to Hospitals regarding updated prescribing information for ceftriaxone with the following new recommendations, which are based on the results of two recent in vitro studies that showed an increased risk of ceftriaxone-calcium precipitates in neonatal plasma.

- Contraindications: Ceftriaxone is contraindicated in neonates if they require (or are expected to require) treatment with calcium-containing intravenous solutions, including continuous calcium-containing infusions such as parenteral nutrition, because of the risk of precipitation of ceftriaxone-calcium.

- Warnings: In patients other than neonates, ceftriaxone and calcium-containing solutions may be administered sequentially if the infusion lines are thoroughly flushed between infusions with a compatible fluid.

- Warnings: Diluents containing calcium, such as Ringer's solution or Hartmann's solution, are not to be used to reconstitute ceftriaxone vials or to further dilute a reconstituted vial for intravenous administration because a precipitate can form. Ceftriaxone must not be administered simultaneously with calcium-containing intravenous solutions, including continuous calcium-containing infusions such as parenteral nutrition via a Y-site, because precipitation of ceftriaxone-calcium can occur.

The Notice states that there have been no reports of interactions between ceftriaxone and oral calcium-containing products or interactions between intramuscular ceftriaxone and calcium-containing products (intravenous or oral).

Ceftriaxone is a long-acting broad spectrum cephalosporin antibiotic for parenteral use. It is indicated for the treatment of lower respiratory tract infections, urinary tract infections, bacterial septicaemia, skin and skin structure infections, bone and joint infections, intra-abdominal infections, and meningitis, when caused by susceptible organisms. Ceftriaxone is also indicated for uncomplicated gonorrhoea and for prophylaxis of patients undergoing certain surgical procedures.

UK (2). The Medicines and Healthcare products Regulatory Agency (MHRA) has emphasized that ceftriaxone should not be given simultaneously with calcium-containing solutions (other than total parenteral nutrition solutions) for intravenous administration because of a risk of calcium precipitation. Ceftriaxone is contraindicated in newborns up to age 28 days who need intravenous treatment with calcium-containing solution including total parenteral nutrition solutions as well as those who have jaundice or who are hypoalbuminaemic or acidotic, because these are conditions in which bilirubin

binding is likely to be impaired. Health-care professionals are also advised that calcium and ceftriaxone may be infused sequentially in patients aged 28 days or older provided that either a) the infusion line is rinsed or flushed between solutions, or b) the infusions are given via different infusion lines at different sites.

The MHRA explains that a review of the available data suggests that newborns (up to age 28 days) are at greater risk of calcium–ceftriaxone precipitation than older patients, particularly if they are premature or have impaired bilirubin binding. The risk of calcium–ceftriaxone precipitation in adults is likely to be low; however, as a precaution, ceftriaxone and calcium should not be administered simultaneously by the intravenous route. The Agency also warns that some total parenteral nutrition solutions contain similar levels of calcium to that in saline solutions such as Ringer's or Hartmann's, and may present a similar degree of risk.

(See WHO Pharmaceuticals Newsletters No. 3, 2009 and No. 4, 2008 for related information in USA and Canada respectively).

***References**:*
(1) Advisories, Warnings and Recalls, Health Canada, 15 October 2009 (www.hc-sc.gc.ca).
(2) Drug Safety Update, MHRA, Volume 3, Issue 3, October 2009 (www.mhra.gov.uk).

Clopidogrel

Drug interaction with omeprazole

USA. The United States Food and Drug Administration (US FDA) has warned health-care professionals and the public about an interaction between clopidogrel (Plavix), an anti-clotting medicine, and omeprazole (Prilosec and Prilosec OTC), a proton pump inhibitor (PPI). New data show that when clopidogrel and omeprazole are taken together, the effectiveness of clopidogrel is reduced. Separating the administration of clopidogrel and omeprazole in time will not reduce this drug interaction.

The US FDA explains that omeprazole inhibits the drug metabolizing enzyme (CYP2C19) which is responsible for the conversion of clopidogrel into its active metabolite. The new studies compared the amount of clopidogrel's active metabolite in the blood and its effect on platelets (anti-clotting effect) in people who took clopidogrel plus omeprazole versus those who took clopidogrel alone. A reduction in active metabolite levels of about 45% was found in people who received clopidogrel with omeprazole compared to those taking clopidogrel alone. The effect of clopidogrel on platelets was reduced by as much as 47% in people receiving clopidogrel and omeprazole together. These reductions were seen whether the drugs were given at the same time or 12 hours apart.

With regard to other medicines that are expected to have a similar effect, the US FDA recommends avoiding the concomitant use of the following medicines and clopidogrel: cimetidine, fluconazole, ketoconazole, voriconazole, etravirine, felbamate, fluoxetine, fluvoxamine, and ticlopidine. In addition, esomeprazole, which is a component of omeprazole, inhibits CYP2C19 and should be avoided in combination with clopidogrel. The Agency states that at this time, it does not have sufficient information about drug interactions between clopidogrel and PPIs other than omeprazole and esomeprazole to make specific recommendations about their co-administration. Health-care professionals and patients are advised to consider all treatment options carefully before beginning therapy.

Health-care professionals are also advised that there is no evidence that other drugs that reduce stomach acid, such as most H2 blockers ranitidine, famotidine, nizatidine, except cimetidine (a CYP2C19 inhibitor) or antacids interfere with the anti-clotting activity of clopidogrel. The clopidogrel label has been updated with new warnings on omeprazole and other medicines that inhibit the CYP2C19 enzyme that could interact with clopidogrel in the same way.

(See WHO Pharmaceuticals Newsletters No. 2, 3, 4 and 5, 2009 for previous information from USA, Canada and New Zealand, Europe, and Ireland respectively).

***Reference**:*
Safety Information, US FDA, 17 November 2009 (www.fda.gov).

Cough and cold medicines

Contraindication recommended

New Zealand. New Zealand Medicines and Medical Devices Safety Authority (Medsafe) has announced that the Cough and Cold Review Group (CCRG) concluded the risk-benefit balance of cough and cold medicines to be unfavourable in children under six years of age. The CCRG has therefore recommended that cough and cold medicines containing the following substances be

contraindicated for use in children under six years of age; brompheniramine, chlorphenamine, dextromethorphan, diphenhydramine, doxylamine, guaifenesin, ipecacuanha, phenylephrine, pholcodine, promethazine, pseudoephedrine, and triprolidine. The CCRG considered that cough and cold medicines containing bromhexine alone, or intra-nasal decongestants (such as oxymetazoline and xylometazoline) should remain available to adults and children over two years of age. Medsafe states that it will work closely with the pharmaceutical industry to implement the recommendations as soon as possible.

(See WHO Pharmaceuticals Newsletters No. 2 and 3, 2009 for new advice on the use of cough and cold medicines in children in Kenya and the UK, Canada and New Zealand, respectively).

***Reference**:*
Prescriber Update Vol. 30, No.4, November 2009 (www.medsafe.govt.nz).

Cyproterone acetate

Risk of meningiomas

UK. The MHRA has advised health-care professionals that patients with existing meningioma or a history of meningioma must not be prescribed cyproterone acetate at doses of 25 mg per day or higher (Cyprostat-50, Cyprostat-100, or Androcur-50). The Agency states that this advice does not apply to medicines that contain low-dose cyproterone acetate such as co-cyprindiol (Dianette). Product information for all products that contain high-dose cyproterone acetate will be updated accordingly.

High-dose cyproterone acetate is indicated for use in the treatment of prostate cancer (dose 50–300 mg per day) and for the control of libido in men with severe hypersexuality or sexual deviation. Lower-dose cyproterone acetate (2 mg) is available for use in women as co-cyprindiol (Dianette) in combination with 35 micrograms ethinylestradiol for the treatment of severe acne that is refractory to prolonged antibiotic therapy, and for moderately severe hirsutism.

The MHRA says that meningiomas are the most common intracranial tumours, with an annual incidence of 6 per 100 000 in the general population. Multiple meningiomas account for approximately 1 to 10% of all cases. Though histologically benign, they can have serious consequences. The occurrence of (multiple) meningiomas has been reported in association with longer-term use (years) of cyproterone acetate at doses of 25 mg/day or higher. According to the Agency, until September 2009, 36 cases of meningioma, of which 19 described multiple meningioma, have been reported worldwide in association with high-dose cyproterone acetate. Of the 36 cases, 32 occurred in women and four in men. Duration of treatment with cyproterone acetate ranged from 4 years to 27 years, and in all but one case it was prescribed at doses higher than 25 mg per day. None of the reported cases had a fatal outcome.

***Reference**:*
Drug Safety Update, MHRA, Volume 3, Issue 3, October 2009 (www.mhra.gov.uk).

Desipramine hydrochloride

Update to prescribing information

USA. Health-care professionals were notified of changes to the Warnings and Overdosage sections of the prescribing information for desipramine hydrochloride (Norpramin). The medicine is indicated for the treatment of depression. The new safety information warn that extreme caution should be used when this medicine is given to patients who have a family history of sudden death, cardiac dysrhythmias or cardiac conduction disturbances; and that seizures precede cardiac dysrhythmias and death in some patients.

Reference:
Safety Information, US FDA 2 December 2009 (www.fda.gov).

Diclofenac sodium

Revisions to the prescribing information to warn of hepatic reactions

USA. Health-care professionals were notified of revisions to the prescribing information to add new warnings and precautions about the potential for adverse liver effects with all products containing diclofenac sodium.

According to Dear Healthcare Professional Letter for diclofenac sodium topical gel (Voltaren® Gel) 1% (non-steroidal anti-inflammatory medicine), in post-marketing reports, cases of drug-induced hepatotoxicity have been reported in the first month but can occur at any time during treatment with diclofenac. Post-marketing surveillance has reported cases of severe hepatic reactions, including liver necrosis, jaundice, fulminant hepatitis with and without jaundice, and liver failure. Some of these reported cases resulted

in fatalities or liver transplantation.

Physicians are advised to measure transaminases periodically in patients receiving long-term therapy with diclofenac, because severe hepatotoxicity may develop without a prodrome of distinguishing symptoms. It is also stated that transaminases should be monitored within 4 to 8 weeks after initiating treatment with diclofenac; however, severe hepatic reactions can occur at any time during treatment with diclofenac.

Reports in WHO Global ICSR database, Vigibase:

Diclofenac sodium

Number of reports with liver and biliary system disorders: 1855

Most reported reactions (number of events):
Hepatic enzymes increased: 159
SGOT increased: 269
SGPT increased: 280
Gamma-GT increased: 133
Hepatic function abnormal: 580
Hepatitis: 507
Hepatitis cholestatic: 167
Bilirubinaemia: 214
Jaundice: 279

Diclofenac

Number of reports with liver and biliary system disorders: 2235

Most reported reactions (number of events):
Hepatic enzymes increased: 227
SGOT increased: 302
SGPT increased: 313
Gamma-GT increased: 160
Hepatic function abnormal: 677
Hepatitis: 601
Hepatitis cholestatic: 193
Bilirubinaemia: 236
Jaundice: 350

Reference:
Safety Information, US FDA
4 December 2009
(www.fda.gov).

Etravirine

Risk of severe skin and hypersensitivity reactions

Canada. Health-care professionals have been informed that severe, potentially life-threatening, and fatal skin reactions have been reported in patients receiving combination therapy that included etravirine (INTELENCE) tablets. These include cases of Stevens-Johnson syndrome, toxic epidermal necrolysis and erythema multiforme. Hypersensitivity reactions have also been reported and were characterized by rash, constitutional findings, and sometimes organ dysfunction, including hepatic failure. The advise emphasizes the importance of immediate discontinuation of etravirine (INTELENCE) in cases where signs or symptoms of severe skin reactions or hypersensitivity reactions develop, including severe rash or rash accompanied by fever, general malaise, fatigue, muscle or joint aches, blisters, oral lesions, conjunctivitis, facial edema, hepatitis, eosinophilia. Health-care professionals are also advised that clinical status including liver transaminases should be monitored and appropriate therapy should be initiated. This safety information will be incorporated in the Canadian Product Monograph.

According to the letter sent to health-care professionals, in Phase 3 clinical trials, Grade 3 and 4 rashes were reported in 1.3% of subjects receiving etravirine (INTELENCE) compared to 0.2% of placebo subjects. A total of 2% of HIV-1-infected patients receiving etravirine (INTELENCE) discontinued from Phase 3 trials due to rash. Rash occurred most commonly during the first six weeks of therapy. The most frequently reported adverse drug reaction (ADR) of at least Grade 2 in severity in the Phase 3 studies was rash (9.0%). Stevens-Johnson syndrome, severe hypersensitivity reaction, and erythema multiforme were reported in < 0.1% of subjects during clinical development with etravirine (INTELENCE). In general, rash was mild to moderate, occurred primarily in the second week of therapy and was infrequent after Week 4. Rash generally resolved within one to two weeks on continued therapy.

(See WHO Pharmaceuticals Newsletter No. 5, 2009 for revisions to the prescribing information for etravirine in USA and the number of reports in the WHO Global Individual Case Safety Reports (ICSR) database, Vigibase).

***Reference**:*
Advisories, Warnings and Recalls, Health Canada
15 October 2009
(www.hc-sc.gc.ca).

Exenatide

Reports of renal failure

USA. The US FDA has notified health-care professionals of revisions to the prescribing information for exenatide (Byetta) to include information on post-marketing reports of altered kidney function, including acute renal failure and insufficiency. Exenatide (Byetta) is an incretin-mimetic that is approved as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

According to the US FDA, from April 2005 through October 2008, the Agency received 78

cases of altered kidney function with 62 cases of acute renal failure and 16 cases of renal insufficiency, in patients using exenatide (Byetta). Some cases occurred in patients with pre-existing kidney disease or in patients with one or more risk factors for developing kidney problems.

Labeling changes include:

- information regarding post-market reports of acute renal failure and insufficiency, highlighting that exenatide (Byetta) should not be used in patients with severe renal impairment (creatinine clearance <30 ml/min) or end-stage renal disease;

- recommendations to health-care professionals that caution should be applied when initiating or increasing doses of exenatide (Byetta) from 5 mcg to 10 mcg in patients with moderate renal impairment (creatinine clearance 30 to 50 ml/min);

- recommendations that health-care professionals monitor patients carefully for the development of kidney dysfunction, and evaluate the continued need for exenatide (Byetta) if kidney dysfunction is suspected while using the product;

- information about kidney dysfunction in the Medication Guide to help patients understand the benefits and potential risks associated with exenatide (Byetta).

Reports in WHO Global ICSR database, Vigibase:

Exenatide

Number of reports with urinary system disorders: 907

Most reported reactions (number of events):
Face oedema: 72
Renal calculus: 65
Micturition frequency: 96
Azotaemia: 76
Renal failure acute: 65
Renal failure chronic: 68
Renal function abnormal: 76
Cystitis: 75

Reference:
Safety Information, US FDA 2 November 2009 (www.fda.gov).

Fosamprenavir calcium

Potential association with myocardial infarction and dyslipidemia

USA. Health-care professionals were notified of a potential association between fosamprenavir calcium (Lexiva) and myocardial infarction and dyslipidemia in HIV infected adults. The product is indicated in combination with other antiretroviral agents for the treatment of HIV infection. The prescribing information for fosamprenavir calcium (LEXIVA) was revised to add myocardial infarction and hypercholesterolemia and to highlight that increases in cholesterol have occurred with treatment. The Dear Healthcare Professional letter recommends the following actions:

- Combination antiretroviral therapy has been associated with redistribution of body fat (lipodystrophy) in HIV-infected patients. Clinical examination should include evaluation for physical signs of fat redistribution.

- Triglyceride and cholesterol levels should be checked prior to initiating therapy with LEXIVA Tablets and Oral Suspension and at periodic intervals during therapy. Appropriate clinical management of lipid disorders should be initiated as required.

- Other modifiable risk factors for cardiovascular disease (such as hypertension, diabetes and smoking) should be monitored in HIV-infected subjects and managed as clinically appropriate.

Reports in WHO Global ICSR database, Vigibase:

Fosamprenavir calcium

Number of reports with metabolic and nutritional disorders as well as myocardial endocardial pericardial and valve disorders: 55

Most reported reactions (number of events):
Lipodystrophy: 9
Weight decrease: 5
Acidosis lactic: 7
Diabetes mellitus: 4
Hyperglycaemia: 9
Hypokalaemia:5
Hypercholesterolaemia:4
Hypertriglyceridaemial:4

Fosamprenavir

Number of reports with metabolic and nutritional disorders as well as myocardial endocardial pericardial and valve disorders: 75

Most reported reactions (number of events):
Cachexia: 4
Lipodystrophy: 11
Phosphatase alkaline increased: 5
Weight decrease: 7
Weight increase: 4
Acidosis lactic: 10

Diabetes mellitus: 5
Hyperglycaemia: 9
Hypokalaemia:7
Hypercholesterolaemia:4
Hypertriglyceridaemial:4

Reference:
Safety Information, US FDA 3 December 2009 (www.fda.gov).

Gadoversetamide

Risk of nephrogenic systemic fibrosis in patients with renal impairment

Canada. Health-care professionals have been advised of product labeling changes of gadoversetamide (Optimark®) due to the risk of nephrogenic systemic fibrosis (NSF) in patients with renal impairment. Gadoversetamide (Optimark®) is a gadolinium (Gd)-based contrast agent (GBCA) that is used to enhance the contrast of magnetic resonance images.

According to the advisory issued by the company, Gadoversetamide (Optimark®) will be contraindicated in patients with 1) acute or chronic severe renal insufficiency (glomerular filtration rate <30 mL/min/1.73m^2), or 2) acute renal insufficiency of any severity due to the hepato-renal syndrome or in the perioperative liver transplantation period. Gadoversetamide (Optimark®) is not recommended for use in children below the age of two years because the safety and efficacy of gadoversetamide, as well as impact of use in patients with an immature kidney function have not been studied.

From 15 August 2006 to 15 October 2009, a total of 93 reports of NSF have been reported worldwide associated with the use of gadoversetamide (Optimark®). It is estimated that 5 134 252 vials of the medicinal product were distributed worldwide from 1 August 2006 to 31 October 2009.

Reference:
Advisories, Warnings and Recalls, Health Canada 12 January 2010 (www.hc-sc.gc.ca).

Iron dextran injection

Change in Boxed Warning

USA. The US FDA and American Regent have notified health-care professionals that anaphylactic-type reactions, including fatalities, have followed the parenteral administration of iron dextran injection. The Boxed Warning has been modified to include the following new information:

- to administer a test dose prior to the first therapeutic dose
- to observe for signs or symptoms of anaphylactic-type reactions during administration of iron dextran injection (Dexferrum)
- to make clear that fatal reactions have occurred following the test dose and have also occurred when the test dose was tolerated.
- to note that patients with a history of drug allergy or multiple drug allergies may be at increased risk of anaphylactic-type reactions

It is recommended that resuscitation equipment and personnel trained in the detection and treatment of anaphylactic-type reactions be readily available during iron dextran injection (Dexferrum) administration.

Reports in WHO Global ICSR database, Vigibase:

Iron dextran

Number of events:
Anaphylactic reaction: 58
Anaphylactic shock: 139
Anaphylactoid reaction: 183

Reference:
Safety Information, US FDA 16 October 2009 (www.fda.gov).

Local anesthetics

Reports of chondrolysis

USA. The US FDA has notified health-care professionals of 35 reports of chondrolysis (necrosis and destruction of cartilage) in patients given continuous intra-articular infusions of local anesthetics (marketed as bupivacaine, chlorprocaine, lidocaine, mepivacaine, procaine, ropivacaine) with elastomeric infusion devices to control post-surgical pain.

According to the Agency, the local anesthetics (with and without epinephrine) were infused for extended periods of time (48 to 72 hours) directly into the intra-articular space using an elastomeric pump. Chondrolysis was diagnosed within a median of 8.5 months after the infusion. Almost all of the reported cases of chondrolysis (97%) occurred following shoulder surgeries. Joint pain, stiffness, and loss of motion were reported as early as the second month after receiving the infusion. In more than half of these reports, the patients required additional surgery, including arthroscopy or arthroplasty. It is not known which specific factor or combination of factors contributed to the development of chondrolysis in these cases. The Agency says that single intra-articular injections of local anesthetics in orthopedic

procedures have been used for many years without any reported occurrence of chondrolysis.

The US FDA emphasizes that local anesthetics are approved as injections for the production of local or regional anesthesia or analgesia, and that the approved drug labels for local anesthetics do not include an indication for continuous intra-articular post-operative infusions or use of infusion devices, such as elastomeric pumps. Health-care professionals are advised not to use elastomeric infusion devices or any other infusion devices for continuous intra-articular infusion of local anesthetics after orthopedic surgery.
Based on the reported cases of chondrolysis above, the US FDA is requiring the manufacturers of local anesthetics and of pumps that may be used to infuse local anesthetics to revise their product labels to warn health-care professionals about this risk.

***Reference*:**
Safety Information, US FDA 13 November 2009 (www.fda.gov).

Natalizumab

Additional measures to better manage risk of progressive multifocal leukoencephalopathy

Europe. The EMEA recommended introducing new measures to minimize the risk of progressive multifocal leukoencephalopathy (PML) associated with natalizumab (Tysabri), following a review by the CHMP on the benefits and risks of natalizumab (Tysabri). The medicine is used to treat relapsing-remitting multiple sclerosis in patients with high disease activity who have failed to respond to treatment with a beta-interferon, or whose disease is severe and progressing rapidly.

The CHMP concluded that the risk of developing PML appears to increase when a patient has been receiving natalizumab (Tysabri) for two years or more. However, the benefits of the medicine continue to outweigh its risks for patients with highly active relapsing-remitting multiple sclerosis, for whom there are few treatment options available. Therefore, the Committee recommended that its marketing authorisation be maintained.
The following measures have been recommended to make sure that patients and doctors are fully aware of the risk of PML.

- The prescribing information for natalizumab (Tysabri) should be updated to reflect the fact that the risk of PML increases after two years of treatment.
- Patients should be fully informed about the risk of PML both by their doctor and in an updated 'patient alert card'.
- Patients should discuss the risks of natalizumab (Tysabri) with their doctor both when treatment starts and again after two years. Forms should be available for patients to sign at both time points to show that they have been informed of the risks associated with the medicine. Completed forms will be stored in the patients' medical notes.
- Patients who develop signs of PML should have their treatment stopped promptly. These patients should be closely monitored for signs of immune reconstitution inflammatory syndrome (IRIS), particularly if they have plasma exchange or immunoadsorption. Intensive care facilities should be available in case patients develop severe IRIS.

The CHMP also confirmed the existing recommendations that patients, and their carers, partners and families be made aware of the symptoms of PML.

The EMEA advises prescribers to closely monitor patients before, during and after treatment with natalizumab (Tysabri) including regular magnetic resonance imaging (MRI) scans, to discuss the risks of PML with their patients before treatment, and to consider whether treatment should continue beyond two years.

(See WHO Pharmaceuticals Newsletters No. 5, 2009 and No. 4, 2006 for reports of PML and the risk management programme for natalizumab in the USA).

Reference:
Press Release, Questions and answers, EMEA, 21 January 2010 (www.emea.europa.eu).

Orciprenaline sulphate

Planned withdrawal following a risk-benefit analysis

UK. The MHRA has announced that orciprenaline sulphate will be withdrawn from the market over the next year because a review recently conducted by the Agency has concluded that the balance of its benefits and risks is no longer favourable. Orciprenaline sulphate (Alupent Syrup) is a non-specific β-agonist indicated for reversible

airways obstruction and suggested for maintenance therapy.

The MHRA explains that an analysis of the available literature demonstrated that orciprenaline sulphate is significantly less efficacious than salbutamol in terms of both the extent and duration of bronchodilation. Yellow Card reports and clinical trial data show a significantly increased incidence of cardiac side effects, mainly palpitations and tachycardia because of its non-selectivity. In addition, clinical trial data show that cardiac side effects occur before maximum bronchodilation is achieved because of its non-selectivity. The Commission on Human Medicines (CHM) has concluded that:

• there should be a planned withdrawal of orciprenaline sulphate from the UK market;
• there are no patient groups for whom transfer to a more-selective β2-agonist would be inappropriate.

Health-care professionals are advised that patients who require a liquid oral formulation of a β-agonist should be switched to a more-selective short-acting β2-agonist such as salbutamol or terbutaline.

Reference:
Drug Safety Update, MHRA, Volume 3, Issue 4, November 2009 (www.mhra.gov.uk).

Oseltamivir

Emergency use in infants less than one year of age

USA. The US FDA has authorized the emergency use of oseltamivir (Tamiflu) in infants less than one year of age in certain cases. The oseltamivir product (Tamiflu for Oral Suspension) is approved for use in treatment and prophylaxis of influenza in pediatric patients one year of age and older. The US FDA notified health-care providers that there are limited data on safety and dosing when considering use of oseltamivir (Tamiflu) in seriously ill, young infants with confirmed 2009 H1N1 influenza, or in one that has been exposed to a confirmed 2009 H1N1 influenza case. Infants should be carefully monitored for adverse events when oseltamivir (Tamiflu) is used. The Agency also warns that oseltamivir (Tamiflu) should not be routinely used for prophylaxis in infants less than three months of age due to extremely limited pharmacokinetic data to guide dosing in this age group. Prophylaxis with oseltamivir (Tamiflu) in infants less than three months of age should be reserved for cases in which the exposure is significant and the risk of severe illness is considered high.

The Agency advises health-care providers that the oral dosing dispenser included in the product package should always be removed and replaced with an appropriate measuring device, when dispensing oseltamivir (Tamiflu oral suspension) for infants younger than one year of age. The pharmacist or other health-care provider should provide a 3 ml or 5 ml oral syringe to correctly measure the dose and counsel the caregiver on how to administer the prescribed dose.

Reference:
Safety Information, US FDA 25 September 2009 (www.fda.gov).

Oseltamivir

Potential medication errors with product for Oral Suspension

USA. The US FDA issued a Public Health Alert to notify prescribers and pharmacists about potential dosing errors with oseltamivir (Tamiflu for Oral Suspension). In the USA, health-care providers usually write prescriptions for liquid medicines in milliliters (mL) or teaspoons, while oseltamivir (Tamiflu) is dosed in milligrams (mg). The dosing dispenser packaged with oseltamivir (Tamiflu) has markings only in 30, 45 and 60 mg. The Agency has received reports of errors where dosing instructions for the patient do not match the dosing dispenser.

The US FDA has alerted that health-care providers should write doses in mg if the dosing dispenser with the medicine is in mg, and that pharmacists should ensure that the units of measure on the prescription instructions match the dosing device provided with the medicine. If prescription instructions specify administration using mL, the dosing device accompanying the product should be replaced with a measuring device (e.g., a syringe) calibrated in mL. The Agency also recommends that prescribers should avoid prescribing oseltamivir (Tamiflu) oral suspension in teaspoons. This can lead to inaccurate dosing. If a prescription is written in teaspoons, the pharmacist should convert the volume to mL and ensure that an appropriate measuring device, such as an oral syringe calibrated in mL, is provided.

References:
Safety Information, US FDA 24 September 2009 (www.fda.gov).

Promethazine injection

Reports of serious tissue injuries

New Zealand. Medsafe has recommended that intravenous promethazine should only be used if the benefits clearly outweigh the risks in each patient. Medsafe warns that promethazine injection is highly caustic to the intima of blood vessels and surrounding tissues. Promethazine injection is approved for the treatment of vomiting, allergic reactions (including anaphylaxis) and to induce sedation.

Medsafe provides the following advice.

1. Deep intramuscular injection is the preferred route of administration of promethazine injection.
2. Promethazine must not be administered subcutaneously or intra-arterially.
3. An alternative medicine should be considered if intravenous administration is required.
4. Promethazine should be administered through large patent veins. Veins in the hand and wrist should be avoided if possible.
5. If intravenous administration is required, the maximum recommended concentration is 25mg/mL and the maximum recommended rate of administration is 25mg/minute. Further dilution and administration over 10 to 15 minutes may reduce the risks even further.
6. The injection should be stopped immediately if pain or a burning sensation occurs.
7. Patients should be advised to seek medical assistance if pain, a burning sensation, swelling or blistering occurs at any time after the administration of intravenous promethazine.

(See WHO Pharmaceuticals Newsletter No. 5, 2009 for revision to the prescribing information for promethazine hydrochloride in USA).

Reference:
Prescriber Update Vol. 30, No.4, November 2009 (www.medsafe.govt.nz)

Sibutramine

Suspension of marketing authorizations recommended in the European Union

Europe (1). The EMEA has announced that the CHMP concluded that the risks of sibutramine-containing medicines are greater than their benefits and recommended the suspension of marketing authorizations for these medicines throughout the European Union. Sibutramine is a serotonin-noradrenaline re-uptake inhibitor (SNRI). Sibutramine-containing medicines are used in the management of obesity, in conjunction with diet and exercise, in obese patients with a body mass index (BMI) ≥ 30 kg/m2, and in overweight patients with a BMI ≥ 27 kg/m2 who also have other risk factors, such as type 2 diabetes or dyslipidaemia.

The review was conducted on data from the Sibutramine Cardiovascular Outcome Trial (SCOUT) as well as other studies on the effectiveness of sibutramine for weight loss. The SCOUT study was designed to determine the impact of weight loss with sibutramine on cardiovascular problems in a large group of overweight and obese patients at high risk for cardiovascular disease. The CHMP noted that the SCOUT study showed an increased risk of serious cardiovascular events (such as heart attack or stroke) in patients with known cardiovascular disease taking sibutramine. The use of sibutramine was not in accordance with the prescribing information for most of the patients in the SCOUT study, as the medicine is contra-indicated in patients with cardiovascular disease. However, the Committee considered that an increased risk can also apply to patients for whom sibutramine can be prescribed because obese and overweight patients are likely to be at risk of cardiovascular disease. The CHMP also noted that the data from available studies show that the weight loss achieved with sibutramine treatment is modest, and that it is not clear if the effect on weight loss can be maintained when sibutramine treatment is stopped. Therefore, the CHMP concluded that the benefits of sibutramine as a weight-loss aid do not outweigh the cardiovascular risks.

The EMEA advises that doctors should stop prescribing sibutramine-containing medicines and that pharmacist should no longer dispense sibutramine-containing medicines. Patients currently taking sibutramine are recommended to make an appointment with their doctor to discuss alternative measures to lose weight.

USA (2). The US FDA has notified health-care professionals and patients that the review of preliminary data from the SCOUT study suggests that patients using sibutramine (Meridia) experienced a higher number of cardiovascular events (heart attack, stroke, resuscitated cardiac arrest, or death) than patients using a placebo (sugar pill). In addition, the review of additional data indicates the increased risk for cardiovascular events with sibutramine occurred only in patients with a history of cardiovascular disease.

Based on those findings, sibutramine will be contraindicated for use in patients with a history of cardiovascular disease, including:

- history of coronary artery disease (e.g., heart attack, angina)
- history of stroke or transient ischaemic attack
- history of heart arrhythmias
- history of congestive heart failure
- history of peripheral arterial disease
- uncontrolled hypertension (e.g., > 145/90 mmHg).

Patients currently using sibutramine are advised to talk with their health-care professional to determine if continued use of sibutramine is appropriate. Health-care professionals are advised to regularly monitor the blood pressure and heart rate of patients using sibutramine. If sustained increases in blood pressure and/or heart rate are observed, sibutramine should be discontinued. The Agency also says that sibutramine should be discontinued in patients who do not lose at least 5% of their baseline body weight within the first three to six months of treatment, as continued treatment is unlikely to be effective and exposes the patient to unnecessary risk.

(Saudi Arabia has informed WHO that the marketing authorizations for sibutramine (Reductil, Sibutral) have been cancelled in the country.)

Reports in WHO Global ICSR database, Vigibase:

Sibutramine

Number of reports with cardiovascular disorders, general, and heart rate and rhythm disorders: 1515

Most reported reactions (number of events):
Arrhythmia: 47
Cardiac arrest: 33
Cardiac failure: 28
Fibrillation atrial: 63
Heart disorder: 25
Hypertension: 641
Hypertension pulmonary: 21
Hypotension: 94
Palpitation: 388
Tachycardia: 337
Tachycardia supraventricular: 32

References:
(1) Press Release, Questions and answers, EMEA, 21 January 2010 (www.emea.europa.eu).
(2) Safety Information, US FDA, 20 November 2009, 21 January 2010 (www.fda.gov).

Sitagliptin

Revisions to prescribing information to include acute pancreatitis

USA. The US FDA notified health-care professionals and patients of revisions to the prescribing information for sitagliptin (Januvia) and sitagliptin/metformin (Janumet) to include information on reported cases of acute pancreatitis in patients using these products. Sitagliptin (dipeptidyl peptidase-4 (DPP-4) inhibitor) is approved as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. The Agency says that 88 post-marketing cases of acute pancreatitis, including two cases of hemorrhagic or necrotizing pancreatitis in patients using sitagliptin, were reported between October 2006 and February 2009.

It is recommended that health-care professionals monitor patients carefully for the development of pancreatitis after initiation or dose increases of sitagliptin or sitagliptin/metformin, and discontinue sitagliptin or sitagliptin/metformin if pancreatitis is suspected. It is noted that sitagliptin has not been studied in patients with a history of pancreatitis. Therefore, it is not known whether these patients are at an increased risk for developing pancreatitis and these medicines should be used with caution and with appropriate monitoring in patients with a history of pancreatitis.

Reference:
Safety Information, US FDA 25 September 2009 (www.fda.gov).

Sleep-aid medicines

Risk of complex sleep-related behaviours

Canada. Health Canada has informed consumers and health-care professionals of changes to the labelling information of sleep aid medicines (sedative-hypnotic medications). Sleep aid medicines are used for short-term treatment of insomnia characterized by difficulty in falling asleep, or waking up often during the night or in the early morning hours. The new labelling describes reports of complex sleep-related behaviours that have occurred while patients were not fully awake, such as talking, walking, cooking, eating, and driving. Patients typically did not remember these events afterwards.

The new labelling also emphasizes the proper use of these medicines. In particular, sleep aid medications should not be taken with alcohol, and patients should not take more

than the prescribed dose. Caution should be used when taking sleep aid medications at the same time as other drugs that can cause drowsiness, such as other tranquilizers or sleeping pills, antihistamines that cause drowsiness, anticonvulsants, painkillers that contain narcotics, and medicines used to treat depression or anxiety.

The sleep-aid medicines with potential risk of complex sleep-related behaviours include flurazepam, nitrazepam, temazepam, triazolam, zopiclone, zolpidem, and zaleplon.

Health Canada advises that discontinuing sleep aid medication should be considered for patients who report complex sleep-related behaviours, due to the risk of harm to the patient and to others. These medications should only be discontinued by an individual after consulting with their health care professional, as abrupt discontinuation may cause symptoms of withdrawal.

(See WHO Pharmaceuticals Newsletter No. 2, 2008 an No. 5, 2007 for warning about sleep disorders with zolpidem in Australia and Sigapore).

Reference:
Advisories, Warnings and Recalls, Health Canada 7 October 2009 (www.hc-sc.gc.ca).

Statins

Updates to product safety information

UK. The MHRA has announced that Summaries of Product Characteristics and Patient Information Leaflets for all statins (HMG-CoA reductase inhibitors: simvastatin, atorvastatin, pravastatin, fluvastatin, and rosuvastatin) will be updated with warnings on adverse reactions. This follows a Europe-wide review of clinical trial data, adverse drug reaction reports and published literature on statins. The MHRA states that the balance of risks and benefits of statins as a class remains positive. However, the review concluded that there is sufficient evidence to support a possible causal relationship between statin use and the following adverse reactions: sleep disturbances, memory loss, sexual dysfunction, depression and interstitial lung disease.

***Reference**:*
Drug Safety Update, MHRA, Volume 3, Issue 4 November 2009 (www.mhra.gov.uk).

Valproate

Increased risk of neural tube defects and other major malformations

USA. The US FDA notified health-care professionals and patients about the increased risk of neural tube defects and other major birth defects, such as craniofacial defects and cardiovascular malformations, in babies exposed to valproate sodium and related products (valproic acid and divalproex sodium) during pregnancy.

According to the Agency, the rates for neural tube defects in babies exposed to valproate during the first trimester (1 in 20 babies) are 30 to 80 times higher than the rate for neural tube defects in the general population in the United States (about 1 in 1500 babies). Data from the North American Antiepileptic Drug (NAAED) Pregnancy Registry show that the rate of major malformations in babies born to women with epilepsy taking valproate (monotherapy) is almost 4 times higher than the rate of major malformations in babies born to women with epilepsy taking a different antiepileptic drug. The NAAED Registry reported a major malformation rate of 10.7% (95% CI 6.3% to 16.9%) in the offspring of women exposed to an average of 1000 mg/day of valproic acid monotherapy during pregnancy (dose range 500 to 2000 mg/day). The major malformation rate among the internal comparison group of 1048 women with epilepsy who received any other antiepileptic drug monotherapy during pregnancy was 2.9% (95% CI 2.0% to 4.1%). There were 16 major malformations in the offspring of 149 women who used valproate during pregnancy, and these malformations included neural tube defects, craniofacial defects, cardiovascular malformations and malformations involving other body systems.

Health-care practitioners are advised to inform women of childbearing potential about these risks, and to consider alternative therapies, especially if valproate is used to treat migraines or other conditions not usually considered life-threatening. The US FDA also states that health-care professionals should inform patients that taking folic acid before and during the first trimester of pregnancy can decrease the risk for congenital neural tube defects. Patients are advised that women of childbearing potential should only use valproate if it is essential to manage their medical condition.

The US FDA has required a patient Medication Guide for each antiepileptic drug, including valproate. The Agency says that

the valproate Medication Guide will explain the benefits and risks of valproate and encourage patients to discuss options with their health-care professional.

(See WHO Pharmaceuticals Newsletter No. 7, 1993 for advice on association of sodium valproate and carbamazepine with neural tube defects in the UK).

Reference:
Safety Information, US FDA
3 December 2009
(www.fda.gov).

Vigabatrin

Risk of movement disorders and MRI abnormalities

UK. The MHRA has informed health-care professionals that movement disorders including dystonia, dyskinesia, and hypertonia have been reported in patients treated with vigabatrin for infantile spasms. The Agency has advised that if new movement disorders occur during treatment with vigabatrin, consideration should be given to dose reduction or a gradual discontinuation of treatment in consultation with specialist advice. Vigabatrin (Sabril) is an antiepileptic indicated, in combination with other antiepileptic drugs, for the treatment of patients with resistant partial epilepsy who have not responded to, or who are intolerant to, all other appropriate drug combinations. Vigabatrin is also indicated as monotherapy in the treatment of infantile spasms (West's syndrome).

The MHRA also explains that a Europe-wide review was conducted and clinical trial data for vigabatrin in infantile spasms provide evidence of brain MRI abnormalities at all doses, but in particular in young infants treated with high doses (≥125 mg/kg/day). These MRI abnormalities were transient and seemed to be dose dependent, and in most patients resolved even if treatment with vigabatrin continued. The review concluded that it is not possible to correlate the MRI findings with the movement disorders based on the current data.

The MHRA says that movement disorders and brain MRI abnormalities will be independently described in the updated product information for vigabatrin to reflect those new data.

Reference*:*
Drug Safety Update, MHRA,
Volume 3, Issue 4
November 2009
(www.mhra.gov.uk).

Warfarin

Product information to be amended

UK. The Medicines and Healthcare products Regulatory Agency (MHRA) has announced that the safety sections in the product information for warfarin, an anticoagulant, will be amended to give clearer, up-to-date advice, following a UK review of safety information for warfarin products. In particular, advice is provided on the following:

- timing of warfarin treatment after ischaemic stroke
- management of the patient before surgical or dental procedures
- patients at particular risk of haemorrhage
- interactions with herbal products, foods, and food supplements
- management of patients with significantly raised INR and/or haemorrhage

The details are available in a public assessment report on MHRA website.

(See WHO Pharmaceuticals Newsletters No.5, 2009, No.6, 2007, No.1, 2006, No.5, 2004 and No1. 2004 for information from New Zealand, Sweden, Canada, Australia, and UK on potential interactions with warfarin as well as No.4, 2007 for labeling update in the USA.)

Reference:
Warfarin: changes to safety information, UK
3 December 2009
(www.mhra.gov.uk)

Alendronate

Risk of low-energy femoral shaft fracture

New Zealand. Medsafe has advised prescribers to consider the risk of atypical stress fractures in patients treated with alendronate who report pain of the subtrochanteric or proximal femoral shaft, based on a number of published case reports. Medsafe recommends that the contralateral femur should be examined if a fracture is suspected, because the reported fractures associated with alendronate were frequently bilateral. Factors which may increase the risk of fractures include: vitamin D deficiency, malabsorption, glucocorticoid use, previous stress fracture, lower extremity arthritis or fracture, extreme or increased exercise, diabetes mellitus, and chronic alcohol abuse. Medsafe also advises that the interruption of bisphosphonate therapy in patients with atypical stress fractures should only be considered following an individual risk-benefit assessment.

(See WHO Pharmaceuticals Newsletter No. 2, 2009 for risk of atypical stress fractures associated with bisphosphonates in the UK).

Reference:
Prescriber Update Vol. 30, No.4, November 2009 (www.medsafe.govt.nz).

Antidepressants

Risk of interactions when switching antidepressants

Australia. The Adverse Drug Reactions Advisory Committee (ADRAC) has warned about possible interactions when switching antidepressants and their possible outcomes, including the development of serotonin syndrome. Antidepressants include selective serotonin reuptake inhibitors (SSRI), tricyclic antidepressants (TCA), monoamine oxidase inhibitors (MAOI), noradrenergic and 5HT1-serotonergic receptor agonists, serotonin and noradrenaline reuptake inhibitors (SNRI), noradrenaline reuptake inhibitors and herbals. ADRAC says that serotonin syndrome is a potential adverse effect of all antidepressants and that it can occur when treatment is not interrupted as well as during switching, particularly in the elderly. The risk of serotonin syndrome increases if there is simultaneous exposure to more than one drug that can cause this syndrome.

ADRAC advises that an appropriate washout or tapering period is necessary when switching between antidepressants. ADRAC also states that factors that should be considered will vary depending on the properties of the antidepressants and the patient's situation including the duration of time the patient has been on the first antidepressant, patient age, other medications and other health issues. If there are concerns about possible withdrawal syndrome, it may be more appropriate to taper the first drug before slowly introducing the second medicine to minimise the risk of withdrawal to the first as well as the risk of adverse reactions due to interactions when the second is introduced.

Reference:
Australian Adverse Drug Reactions Bulletin, Volume 28, Number 5, October 2009 (www.tga.gov.au)

Bisphosphonates

Review on the risk of osteonecrosis of the jaw

Europe. The European Medicines Agency (EMEA) has announced that the Agency's Committee for Medicinal Products for Human Use (CHMP) concluded that there is an increased risk of osteonecrosis of the jaw in patients using bisphosphonates (including alendronic acid, clodronic acid, etidronic acid, ibandronic acid, neridronic acid, pamidronic acid, risedronic acid, tiludronic acid and zoledronic acid). However, further studies should be carried out to better identify the factors that increase the risk and the measures needed to minimise it.

The CHMP has agreed on the following four areas:

- the criteria that define osteonecrosis of the jaw related to bisphosphonates;
- how bisphosphonates may cause osteonecrosis of the jaw;
- whether the risk of osteonecrosis of the jaw is greater with some bisphosphonates or for some groups of patients;
- the measures that could be taken to minimise this risk.

With regard to the definition of osteonecrosis of the jaw related to bisphosphonates, the CHMP has defined it as an area of exposed or dead bone in the jaw that has lasted for more than eight weeks, in a patient who has been exposed to a bisphosphonate and has not had radiation therapy on the jaw.

With regard to possible underlying mechanism, the CHMP considered that further studies are required and a suitable experimental model should be developed.

With regard to risk stratification, the Committee noted that:

- the risk of osteonecrosis of the jaw is greater in cancer patients receiving intravenous bisphosphonates than in patients being treated for non-cancer indications, such as osteoporosis;
- the risk appears to be low in patients taking bisphosphonates by mouth.

The CHMP concluded that further research on risk factors is needed, though the most important risk factors seem to be the potency of the bisphosphonate used, the dose and how it is given.

With regard to risk minimization measures, the CHMP concluded that further data are needed to determine the precise measures that could minimise the risk of osteonecrosis of the jaw, including looking at how intravenous bisphosphonates should be given, and looking into the risk of osteonecrosis of the jaw in patients taking bisphosphonates by mouth for long periods. The CHMP also noted that other possible risk factors for developing osteonecrosis of the jaw should be considered, such as gender, genetic factors, smoking and other treatments or diseases that the patient has, as well as the type of cancer a patient has and how long they have had it.

The following are recommended.

- Before taking any decisions concerning treatment with bisphosphonates, prescribers should take the risks and benefits for each individual patient into account.
- Prescribers should ensure that patients with cancer go to their dentist for a check-up and find out if they need any dental treatment before they start taking a bisphosphonate. They should also ensure that patients who do not have cancer go to their dentist for a check-up if their dental health is poor.
- During treatment with bisphosphonates, patients should maintain good oral hygiene, go for routine dental check-ups and report any symptoms in the mouth such as loose teeth, pain or swelling.
- Dentists should be aware of the risks in patients taking bisphosphonates and should keep dental treatment as conservative and preservative as possible.
- It is essential that prescribers, dentists and patients work together to manage the risk of osteonecrosis of the jaw.
- Patients who have any questions or concerns should speak to their doctor or dentist.

Reference:
Questions and answers on the review of bisphosphonates and the risk of osteonecrosis of the jaw, CHMP opinion, EMEA 24 September 2009 (www.emea.europa.eu)

Colchicine

Risk of serious and fatal toxicity in overdose

UK. The MHRA reminded health-care professionals that colchicine has a narrow therapeutic window and is extremely toxic in overdose. Patients at particular risk of toxicity are those with renal or hepatic impairment, gastrointestinal or cardiac disease, and patients at extremes of age. There is often a delay of up to 6 hours before toxicity is apparent, and some features of toxicity may be delayed by one week or longer. Early features of toxicity (up to one day after ingestion) include nausea, vomiting, abdominal pain, and diarrhoea. Diarrhoea may be profuse and bloody, and the patient may present with electrolyte disturbances and hypovolaemic shock. Features after one to seven days include confusion, decreased cardiac output, cardiac arrhythmias, renal and hepatic impairment, respiratory distress, hyperpyrexia, and bone-marrow depression. This can progress in severe cases to include multiple organ failure with accompanying bone-marrow aplasia, convulsions, coma, rhabdomyolysis, and disseminated intravascular coagulation. Colchicine is licensed for the treatment of acute gout, but only in cases where non-steroidal anti-inflammatory drugs are not tolerated or ineffective. It is also licensed for short-term prophylaxis during initial therapy with other drug treatments.

For the initial management of colchicine overdose, health-care professionals are advised to consider oral activated charcoal as well as general symptomatic and supportive measures as indicated by the patient's clinical condition, including monitoring of vital signs, electrocardiography, and haematological and biochemical indices.

(See WHO Pharmaceuticals Newsletter Nos 1, 2006 and 4, 2006 for related warnings in New Zealand)

***Reference**:*
Drug Safety Update, MHRA, Volume 3, Issue 4, November 2009 (www.mhra.gov.uk).

Deferasirox

Potential revisions to the product information

Canada (1). Health-care professionals have been advised about renal events and gastrointestinal haemorrhage associated with deferasirox

(Exjade) in patients diagnosed with myelodysplastic syndrome (MDS) and in elderly patients. Deferasirox (Exjade) is indicated in the management of chronic iron overload in patients with transfusion-dependent anaemias aged 6 years or older as well as those aged 2 to 5 who cannot be adequately treated with deferoxamine.

A letter issued by the company to health-care professionals highlights the following points.

- Review of adverse events for patients treated with deferasirox (Exjade) suggests a greater risk of kidney failure, gastrointestinal hemorrhage (potentially fatal) and deaths in patients with MDS and in elderly patients compared to younger patients with other chronic anaemias such as β-thalassaemia and sickle cell disease.
- The company has proposed changes to the Canadian Product Monograph, including a contraindication in high risk MDS patients and those with advanced malignancies because these patients are not likely to benefit from iron chelation therapy due to the expected rapid progression of their disease.
- Risk factors for kidney failure include pre-existing compromised renal function, and it is therefore recommended that creatinine clearance (and/or serum creatinine) be assessed twice before initiating therapy. Weekly monitoring of creatinine clearance (and/or serum creatinine) is recommended in the first month after initiation or modification of therapy, and monthly thereafter. In addition to the existing creatinine clearance contraindication of <60 mL/min, the company has proposed to include a contraindication of serum creatinine >2 times the age-appropriate upper limit of normal.

- Gastrointestinal hemorrhage is a known adverse reaction of deferasirox (Exjade). There have been rare reports of fatal gastrointestinal hemorrhage, especially in elderly patients who had advanced haematologic malignancies and/or low platelet counts.

USA (2). The US FDA has notified health-care professionals of an ongoing review of safety issues with deferasirox (Exjade). Deferasirox (Exjade) is an iron chelating agent that is approved for use in the treatment of patients aged two and older with chronic anaemia and iron overload as a result of receiving blood transfusions. The Agency is reviewing adverse event information for deferasirox (Exjade) from a database that tracks all patients who are prescribed the medicine and a company-sponsored global safety database. The Agency explains that this information suggests there may be a greater risk for adverse events such as kidney failure, gastrointestinal hemorrhage (potentially fatal bleeding) and deaths in patients with myelodysplastic syndrome (MDS) compared to patients without these conditions. Many of these patients are over sixty years old. The number of deaths and serious adverse events seem to be fewer in younger patients with other chronic anemias such as β Thalassemia and Sickle Cell disease.

The US FDA is working with the company with regard to potential revisions to the prescribing information to warn health-care professionals about the possible risks in certain patients and to ensure that the benefits of the medicine outweigh the potential risks, particularly in older patients and patients with MDS.

(See WHO Pharmaceuticals Newsletter No. 2, 2008 for reports of hepatic failure in Canada and the USA, and No. 2, 2007 for reports of renal failure in Canada and Switzerland.)

References:

(1) Advisories, Warnings and Recalls, Health Canada 3 December 2009 (www.hc-sc.gc.ca).

(2) Safety Information, US FDA 25 September 2009 (www.fda.gov).

Finasteride

Potential risk of male breast cancer

UK. The MHRA warned that cases of male breast cancer have been reported in clinical trials and during post-marketing use with finasteride treatment. Finasteride is an inhibitor of type II 5α-reductase, which metabolises testosterone into the more potent androgen, dihydrotestosterone (DHT). In the UK, 5 mg finasteride (Proscar) is used for the treatment and control of benign prostatic hyperplasia, and 1 mg dose (Propecia) is indicated for the treatment of men with androgenetic alopecia. According to the *Drug Safety Update*, up to November 2009, 50 cases of male breast cancer have been reported worldwide with 5 mg finasteride and 3 cases with the 1 mg dose. A review of available data suggests that an increased risk of breast cancer with finasteride cannot be excluded.

The MHRA advises patients to promptly report to their doctor any changes in their breast tissue such as lumps, pain or nipple discharge.

Reference:
Drug Safety Update, MHRA, Volume 3, Issue 5 December 2009 (www.mhra.gov.uk)

Gadolinium-containing contrast agents

Recommendations to minimise risk of nephrogenic systemic fibrosis

Europe. EMEA has adopted a set of recommendations aimed at minimising the risk of nephrogenic systemic fibrosis (NSF) with gadolinium-containing contrast agents. Gadolinium-containing contrast agents are used in patients undergoing magnetic resonance imaging (MRI) or magnetic resonance angiography (MRA) scans.

The CHMP conducted a review on gadolinium-containing contrast agents and NSF, and made recommendations according to their risk classification.

For high-risk gadolinium-containing contrast agents (Optimark, Omniscan, Magnevist, Magnegita and Gado-MRT ratiopharm), the CHMP recommended contraindications in patients with severe kidney problems, in patients who are scheduled for or have recently received a liver transplant and in newborn babies up to four weeks of age. To minimise the risk of using these high-risk agents in patients with unknown kidney problems, the CHMP advised that patients should always be screened for kidney problems using laboratory tests before use. It is also recommended that women should discontinue breastfeeding for at least 24 hours after a scan.

For medium- (Vasovist, Primovist and MultiHance) and low-risk agents (Dotarem, ProHance and Gadovist), the CHMP recommended adding new warnings in the prescribing information concerning their use in patients with severe kidney problems and patients receiving a liver transplant. Screening patients for kidney problems using laboratory tests is generally recommended before administration of these gadolinium-containing contrast agents. The decision to continue or suspend breastfeeding for at least 24 hours after a scan should be taken by the doctor and the mother.

The CHMP recommended that the prescribing information of all gadolinium-containing contrast agents should include:

- a warning that the elderly may be at particular risk of NSF due to impaired ability of their kidneys to clear gadolinium from the body;
- a statement that there is no evidence to support the initiation of haemodialysis to prevent or treat NSF in patients not already undergoing haemodialysis;
- a statement that the type and dose of contrast agent used should be recorded.

(See WHO Pharmaceuticals Newsletter No. 1, 2008 and No.3, 2007 for warning about risk of nephrogenic systemic fibrosis in Australia and USA respectively).

***Reference**:*
Press Release, EMEA 20 November 2009 (www.emea.europa.eu).

H1N1 pandemic vaccines

Reports of suspected adverse reactions

Europe (1). The European Medicines Agency issues pandemic pharmacovigilance weekly updates that include a summary of the adverse drug reactions reported after the use of centrally authorised pandemic vaccines (Celvapan, Focetria and Pandemrix) and antivirals (Tamiflu).

According to the ninth weekly update, as of 1 February 2010, at least 35.7 million people, including at least 261 000 pregnant women, had been vaccinated with one of the three centrally authorised vaccines, in the European Economic Area. As of 24 January 2010, a total of 12 705 case reports (432 reports for Celvapan, 2837 reports for Focetria, 9449 reports for Pandemrix) had been received by EudraVigilance since the authorisation of those three vaccines. With regard to oseltamivir (Tamiflu), from 1 April 2009 to 24 January 2010, a total of 969 reports worldwide were received by EudraVigilance.

The vast majority of the adverse reactions that had been reported as of 24 January 2010 are considered to be non-serious. The benefit-risk balance of the pandemic vaccines and antivirals being used for the current H1N1 influenza pandemic continues to be positive.

The safety profile of the three pandemic vaccines have been reassessed based on the periodic safety update reports submitted by the companies. Following evaluation, it was concluded that the benefit-risk balance remains positive. According to the sixth update,

regarding Celvapan, new safety concerns, including convulsions, pain in extremity and influenza-like symptoms. are being considered for addition to the product information.

Details of the reported reactions are available on the EMEA website. (www.emea.europa.eu).

The EMEA has warned that young children may experience fever after their second dose of the pandemic influenza vaccine Pandemrix (2). This follows the review by the CHMP of new data on the use of a second dose of the pandemic vaccine Pandemrix in children aged from 6 months to 3 years. The Agency also noted that the second dose increases the immune response against pandemic influenza.

According to the Agency, the data showed a higher proportion of children developing fever (temperature above 38°C, when measured under the armpit) after the second dose of Pandemrix, compared with after the first. Moreover, there was more soreness at the site of injection and more general symptoms such as drowsiness, irritability and loss of appetite after the second dose. The study also indicated that a single dose of vaccine triggered a good immune response in young children, but that the second dose further increased the immune response.

EMEA advises that parents and carers of young children (below 6 years of age) vaccinated with Pandemrix should be aware that fever may occur, and that this fever can be high (above 38ºC). Prescribers and parents/carers should monitor the temperature of the vaccinated child and, if necessary, take measures to lower the fever (e.g. giving an antipyretic such as paracetamol). EMEA has recommended that this information be included in the prescribing information, and be taken into consideration when deciding whether to give a second dose to young children.

Ireland (3). The Irish Medicines Board (IMB) provides updates on national monitoring experience with Pandemic H1N1 vaccines (Pandemrix and Celvapan) on a regular basis. According to the 4 February 2010 update, it is estimated that approximately 1.6 million doses have been distributed and some 850 000 doses have been administered in Ireland. Up to 2 February 2010, the IMB received 1291 reports of suspected adverse reactions to the two Pandemic H1N1 vaccines (840 reports for Pandemrix, 430 reports for Celvapan, brand unknown in 21 cases). The reports remain consistent with the expected pattern of adverse effects for the vaccines. The balance of risks and benefits for these vaccines (Celvapan and Pandemrix) remains positive. The IMB advises health-care professionals and parents to monitor the temperature of the vaccinated child and to take measures, if necessary, to lower the fever (e.g. giving an antipyretic such as paracetamol).

Details of the reported reactions are available on the IMB website (www.imb.ie).

Switzerland (4). The Swiss Agency for Therapeutic Products (Swissmedic) updates information on reports of suspected adverse events following vaccination with pandemic influenza vaccines. According to the 28 January 2010 update, as of 22 January 2010, 286 250 doses of Focetria®, 1 697 300 doses of Pandemrix® and 985 330 doses of Celtura® have been delivered. It is not known how many doses have been administered. Up to 22 January, there have been 424 reports for Pandemrix®, 54 reports for Focetria®, and 29 reports for Celtura®. The majority of reports are self-limited reactions at the injection site, as well as generalized reactions such as headache, fever, muscle aches and joint pain.
Swissmedic states that the reported adverse reactions correspond with those described in clinical trials and with the profile from post-marketing experience with seasonal influenza vaccines. The reported adverse reactions of the pandemic influenza vaccines correspond to those observed in other countries using the same vaccine products.
Details of the reported reactions are available on the Swissmedic website (www.swissmedic.ch).

References:

(1) Pandemic pharmacovigilance weekly update, EMEA (www.emea.europa.eu).
(2) Press Release, Questions and Answers, EMEA 4 December 2009 (www.emea.europa.eu).
(3) Update on National Monitoring Experience with Pandemic H1N1 Vaccines, IMB (www.imb.ie).
(4) Latest information about vigilance for H1N1 flu vaccines in Switzerland, Swissmedic, (www.swissmedic.ch).

Human insulin and insulin analogues

Review on a possible increased risk of cancer

Japan. The Ministry of Health, Labour and Welfare (MHLW), Japan published results of a review on possible association of human insulin and insulin analogues (insulin aspart, insulin

glargine, insulin glulisine, insulin detemir and insulin lispro) with an increased risk of cancer. The review was conducted by the Pharmaceuticals and Medical Devices Agency (PMDA). PMDA has concluded that, at this time, no additional safety measures are needed for those insulin preparations for the following reasons.

Association between insulin preparations in general and risk of cancer

- In the epidemiological studies regarding an increased risk of cancer in association with insulin preparations, some studies showed an increased risk of cancer, whereas others did not. There were limitations in most of those studies, for example, insufficient adjustment for confounding factors such as family history. Therefore, they can not be considered to provide sufficient evidence that confirms a causal relationship between insulin preparations and an increased risk of cancer.
- The non-clinical data submitted at the time of application for approval of insulin analogues demonstrated that cell proliferation induced by insulin analogues is of a similar magnitude to that induced by human insulin. Therefore, it was concluded at the time of approval review, that it was not necessary to include any specific precaution in the package insert. Also, a review of several reports published after the approval did not lead to a change in this conclusion.
- Package inserts used in foreign countries do not currently include any information giving precaution against an increased risk of cancer.

Association between insulin glargine and risk of cancer

- Regarding insulin glargine, some epidemiological studies showed an increased risk of cancer associated with insulin glargine, compared with other insulin preparations, whereas other studies did not. Those results were found to be inconsistent.
- Non-clinical studies showed that cell proliferation induced by insulin glargine is of a similar magnitude to that induced by human insulin. Furthermore, when compared with cell proliferation induced by other insulin analogues, insulin glargine was not considered to be associated with an increased risk of cancer.
- Regarding an possible increased risk of cancer in association with insulin glargine, EMEA does not consider it necessary at present to take any action, and package inserts used in foreign countries do not include any information giving precaution against an increased risk of cancer.

Based on the above, PMDA states that it is not necessary to alert about the risk of cancer, given that the association between insulin preparations and cancer has not been suggested.

(See WHO Pharmaceuticals Newsletter No. 4, 2009 for risk of cancer associated with insulin glargine in Europe and the USA).

Reference:
Pharmaceuticals and Medical Devices Safety Information No.263, MHLW, November 2009 (www.pmda.go.jp/english).

Immune globulin

Risk of hemolytic reactions with intravenous immune globulin

Canada. Health Canada has warned health-care professionals to be aware of haemolysis associated with the use of intravenous immune globulin (IVIG). Haemolysis is a rare but well-described adverse reaction associated with IVIG therapy. IVIG products are indicated as replacement therapy in cases of primary and secondary immune deficiencies, for idiopathic thrombocytopenic purpura and for the treatment of chronic inflammatory demyelinating polyneuropathy.

According to the Canadian Adverse Reaction Newsletter, a standardized case definition of IVIG-associated haemolysis has been proposed to assist in the investigation and reporting of suspected cases. Using this definition, Health Canada analyzed all reports of haemolysis (reported as hemolytic anemia, haemolysis, spherocytic anaemia, haemolytic reaction, decreased haemoglobin and haemolytic transfusion reaction) suspected of being associated with the use of IVIG that were received from 1 December 2006 to 31 March 2009. Of the 81 reports received, 20 involved cases that met the criteria for IVIG-associated haemolysis, 23 had an alternate possible cause for anaemia, and 38 lacked the required laboratory work. Health

Canada states that risk factors for haemolysis included blood group A (in 14 cases) or AB (in 6 cases) and a high total dose of IVIG (≥ 2 g/kg). Of the adverse reaction reports that included the total dose in grams per kilogram, 85% of the patients (11 out of 13) received a total dose of ≥ 2 g/kg.

(See WHO Pharmaceuticals Newsletter No. 3, 2009 for reports of severe adverse reactions with intravenous immunoglobulin in Australia).

Reference:
Canadian Adverse Reaction Newsletter Volume 19, Issue 4, Health Canada, October 2009 (www.hc-sc.gc.ca).

Lamotrigine

Risk of serious skin reactions, including toxic epidermal necrolysis and Stevens Johnson's syndrome

New Zealand. Medsafe emphasizes the importance of adhering to the recommended dose guidelines when prescribing lamotrigine to patients already taking sodium valproate, because of the risk of serious skin reactions. The CARM database contains reports of toxic epidermal necrolysis (TEN) and Stevens Johnson's syndrome (SJS) in patients taking concomitant lamotrigine and sodium valproate. Medsafe explains that risk factors included exceeding the recommended starting dose of lamotrigine or the rate of dose escalation. Lamotrigine is approved as adjunctive therapy in adults and children with epilepsy, and for the prevention of mood disorders in adults with bipolar disorder. In adult patients already taking sodium valproate, the starting dose of lamotrigine is 12.5 mg/day (or 25 mg on alternate days) for 14 days, increased to 25 mg/day for a further 14 days. The dose of lamotrigine can thereafter be increased by 25–50mg/day every 7 to 14 days.

According to Medsafe, the incidence of serious skin reactions (including TEN and SJS) in clinical trials using recommended lamotrigine dosing is approximately 1 in 500 epilepsy patients and 1 in 1000 patients with bipolar disorder. The incidence of serious skin reactions is greater in children with estimates ranging from 1 in 300 to 1 in 100 children. Serious skin reactions generally occur within 8 weeks of commencing lamotrigine therapy. The risk is increased by high initial doses of lamotrigine, exceeding recommended doses, rapid dose escalation and concomitant use of sodium valproate.

Reference:
Prescriber Update Vol. 30, No.4, November 2009 (www.medsafe.govt.nz).

Metoclopramide

Risk for development of movement disorders including tardive dyskinesia

Australia. ADRAC warns about the risk of extrapyramidal acute dystonic reactions and tardive dyskinesia associated with metoclopramide. Metoclopramide is a selective D2 dopamine receptor antagonist that is a long-established antiemetic and antinauseant.

Acute dystonic reactions generally occur within 72 hours of exposure to metoclopramide and affect younger population. ADRAC has received 111 reports of acute dystonic reactions associated with metoclopramide. The age range is predominantly from a few months through childhood to young adults, with less than 10% in those over the age of 40.

ADRAC has received 11 reports of tardive dyskinesia in association with metoclopramide-containing medicines, of which 9 occurred in women 68 years or older. Where details of time to onset from drug initiation were provided, it was generally more than one year. The risk of developing tardive dyskinesia with metoclopramide increases with age, female gender and duration of treatment/number of doses.

Prescribers are reminded of the risk for development of tardive dyskinesia in patients receiving long-term metoclopramide treatment, particularly in the elderly. Prescribers are also advised that all patients taking metoclopramide should be regularly reviewed to determine if continued treatment is necessary.

(See WHO Pharmaceuticals Newsletter No. 2, 2009 for warning against chronic use in USA and reports in WHO Global ICSR database.)

Reference:
Australian Adverse Drug Reactions Bulletin, Volume 28, Number 5, October 2009 (www.tga.gov.au)

Phenytoin

Risk of Stevens-Johnson syndrome and presence of the HLA-B*1502 allele

UK. The MHRA has advised health-care professionals that the human leukocyte antigen (HLA) allele *HLA-B*1502* may be associated with an increased risk of developing Stevens-Johnson syndrome (SJS) in individuals of

Thai and Han Chinese ethnic origin when treated with phenytoin. The Agency recommends that if these patients are known to be *HLA-B*1502*-positive, phenytoin should be avoided when alternative therapy can be given. Phenytoin is an antiepileptic drug, and is one of the most common causes of antiepileptic-related cutaneous adverse reactions, including SJS and toxic epidermal necrolysis (TEN).
According to the *Drug Safety Update*, a recent study has shown a significant association between the *HLA-B*1502* allele and phenytoin-induced SJS in patients of Thai or Han Chinese ethnic origin. However, available data are too limited to recommend screening of patients of Thai or Chinese ethnic origin for presence of the *HLA-B*1502* allele before starting phenytoin treatment.

MHRA states that in the Caucasian and Japanese population, the frequency of *HLA-B*1502* is extremely low, and thus it is not possible at present to conclude on risk association between phenytoin-induced SJS and the presence of this allele. Adequate information about risk association in other patients of other ethnic origin is currently not available.

*(See WHO Pharmaceuticals Newsletter No. 5&6, 2008 for caution against use in HLA-B*1502-positive patients in the USA).*

Reference:
Drug Safety Update, MHRA, Volume 3, Issue 6 January 2010 (www.mhra.gov.uk).

Rituximab

A third case of progressive multifocal leukoencephalopathy

Canada and USA. Health Canada and the companies have warned about association of rituximab (RITUXAN) with progressive multifocal leukoencephalopathy (PML). Rituximab (RITUXAN) is authorized for the treatment of B-cell non-Hodgkin's Lymphoma, previously untreated B-cell chronic lymphocytic leukemia, stage B or C, and rheumatoid arthritis in combination with methotrexate to reduce signs and symptoms in adult patients with moderately to severely active rheumatoid arthritis who have had an inadequate response or intolerance to one or more tumour necrosis factor (TNF) inhibitor therapies.

Health-care professionals have been notified that a third case of PML has been reported in a patient with rheumatoid arthritis treated with rituximab (RITUXAN). This is the first case of PML in a patient with rheumatoid arthritis receiving rituximab (RITUXAN) who has not been previously treated with other potent biologic immuno modulating therapies. While the potential mechanism of rituximab (RITUXAN) in the development of PML is unclear, a contributory role is possible. Available information to date suggests that patients with rheumatoid arthritis who receive rituximab (RITUXAN) may have an increased risk of PML. It is advised that physicians should consider PML in any patient being treated with rituximab (RITUXAN) who presents with new onset neurologic manifestations (i.e. cognitive impairment, motor deficit, speech and vision impairment). In patients who develop PML, rituximab (RITUXAN) should be discontinued.

References:
Advisories, Warnings and Recalls, Health Canada 21 October 2009 (www.hc-sc.gc.ca).
Safety Information, US FDA 23 October 2009 (www.fda.gov).

SSRIs/SNRIs and thiazide diuretics

Medicines most often associated with hyponatreamia

New Zealand. The November 2009 issue of Prescriber Update describes the results of examination of recent reports with hyponatraemia in the database of the New Zealand Centre for Adverse Reactions Monitoring (CARM). Medicines most often associated with hyponatraemia, which is defined as plasma sodium < 135mmol/L, were selective serotonin or noradrenaline reuptake inhibitors (SSRIs/SNRIs) and thiazide diuretics. Other medicines reported more than once in 2007 and 2008 were anticancer agents, proton pump inhibitors, sodium valproate and ACE inhibitor/diuretic combinations. Carbamazepine has also been frequently associated in the database. Medicine-related hyponatraemia occurs most often in the elderly early in the course of treatment. The mechanism is most often syndrome of inappropriate antidiuretic hormone secretion (SIADH) or renal loss.

In most of the serious symptomatic reports that CARM received, more than one hyponatraemic medicine was associated. Reports for three patients indicated that they each had persistent mild to

moderately low plasma sodium levels (128 to 133mmol/L) while taking two hyponatraemic medicines. Following addition of a third hyponatraemic agent, a much more profound fall ranging from 104 to 121mmol/L occurred.

It is advised that plasma sodium should be measured shortly after starting potentially hyponatraemic medicines, especially SSRIs or diuretics. Measurements should be repeated both before and after adding another hyponatraemic medicine. If there is mild persistent hyponatraemia, the addition of further medicines may lead to a more profound and symptomatic reaction.

Reference:
Prescriber Update Vol. 30, No.4, November 2009 (www.medsafe.govt.nz).

Zanamivir

Warning against reconstitution in liquid formation

Canada and USA. Health Canada, the US FDA and GlaxoSmithKline have notified health-care professionals of a report of the death of a patient with influenza who received zanamivir (Relenza Dry Powder for Inhalation) which was solubilized and administered by mechanical ventilation. Zanamivir (Relenza) is a neuraminidase inhibitor indicated for treatment of uncomplicated illness due to influenza A and B in patients seven years of age or older who have been symptomatic for no more than two days. Zanamivir (Relenza) is also indicated for prophylaxis of influenza in patients seven years of age or older.

Health-care providers are alerted to the following information.

- Zanamivir (Relenza Dry Powder for Inhalation) is not intended to be reconstituted in any liquid formulation and is not recommended for use in any nebulizer or mechanical ventilator.
- Zanamivir (Relenza) for nebulization has not been approved by any regulatory authority and the safety, effectiveness and stability of zanamivir use by nebulization have not been established.

The letters sent to health-care professionals say that zanamivir (Relenza Dry Powder for Inhalation) should only be used as directed in the prescribing information by using the Diskhaler inhalation device provided with the medicine. The product is a mixture of zanamivir active substance and lactose drug carrier. There is risk that the lactose sugar in this formulation can obstruct proper functioning of mechanical ventilator equipment.

References:
Advisories, Warnings and Recalls, Health Canada 3 November 2009 (www.hc-sc.gc.ca).
Safety Information, US FDA 9 October 2009 (www.fda.gov)

Serious skin disorders associated with medicines

Japan. MHLW issued a summary of cases of Stevens- Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) that were reported to the Ministry between 1 October 2005 and 31 July 2009. There were 2370 cases of adverse drug reactions reported as SJS or TEN (2.2% out of a total of 110 023 cases of adverse reactions reported for the period). Of these, 146 cases (6.2%) were reported to be possibly associated with over-the-counter drugs. The outcomes in the 2370 cases of SJS or TEN were as follows: 1373 (57.9%) recovered or improved; 85 (3.6%) did not recover; 84 (3.5%) had sequelae; 239 (10.1%) died; and outcome was unknown in 589 (24.9%).

There were 400 active ingredients associated with SJS or TEN. Most frequently reported medicines were allopurinol, carbamazepine, loxoprofen sodium hydrate, acetaminophen, diclofenac sodium, zonisamide, salicynamide/acetaminophen/anhydrous caffeine/promethazine methylenedisalicylate, clarithromycin, phenobarbital, and levofloxacin hydrate.

MHLW warns that although SJS and TEN are rare, these skin disorders may occur irrespective of the medicine administered. The Ministry states that when rash and accompanying hyperthermia develop after administration of medicines and SJS or TEN is suspected, the medicine should be discontinued and the patient should be promptly referred to a dermatologist.

Reference:
Pharmaceuticals and Medical Devices Safety Information No.261, MHLW, September 2009 (www.pmda.go.jp/english/)

FEATURE

Prequalification of Quality Control Laboratories

Prequalification of Medicines Programme, WHO

Background

In order to achieve the Millennium Development Goals it is necessary to increase the availability and supply of good quality Essential Medicines in countries that need these medicines. However, several international funders and suppliers of these medicines have faced difficulties in monitoring the quality of these medicines because quality control laboratories are either not available or the quality of their work cannot be assured in those very countries where the medicines are to be used. Thus, international donors and suppliers have often had these medicines analysed in quality control laboratories situated in other countries, in Europe or Northern America. This is not consistent with WHO's programmes for sustainable development because it does not build capacity on the ground. The World Health Organization (WHO) in collaboration with UNAIDS, UNICEF, UNFPA, the Global Fund, UNITAID and with the support of the World Bank started the prequalification of quality control laboratories in 2004. The objective was to help build quality control laboratories that meet recommended international norms and standards for the analysis of products prequalified or being considered for prequalification by the WHO Medicines Prequalification (WHO PQ) Programme. In the first phase WHO invited Expressions of Interest from Quality Control Laboratories in Africa committed to providing a service of testing of pharmaceutical products, including but not limited to HIV/AIDS, Tuberculosis and Malaria products at affordable prices, to UN agencies. In September 2007 the scope of the procedure was extended and currently the invitations are not limited to quality control laboratories from Africa or any other specific region. WHO, however, reserves the right to prioritize the assessment of national quality control laboratories or those laboratories which provide testing services to the government in the respective country, and quality control laboratories in areas where UN agencies and their partners (such as UNITAID) identify the need for quality testing.

The invitation for Expression of Interest to participate in the prequalification procedure is published at WHO web site (1).The invitation is published in accordance with the *Procedure for assessing the acceptability, in principle, of quality control laboratories for use by United Nations agencies*, adopted by the WHO Expert Committee on Specifications for Pharmaceutical Preparations in 2003 and subsequently amended in 2007 (2). Participation in the prequalification procedure is voluntary and any laboratory (governmental or private) can participate. Currently, the participation is free of charge, but the procedure enables WHO to charge for the quality assessment procedure on a cost-recovery basis.

General information

The procedure established by WHO for assessment of quality control laboratories includes the evaluation of the information submitted by a laboratory (Laboratory Information file, LIF) and an on-site inspection of the laboratory to assess the compliance with the guidelines on *Good Practices for National Pharmaceutical Control Laboratories* (3) and *Good Manufacturing Practices* (4) as recommended by WHO for such laboratories. All the related guidelines are published at the WHO web site (5). Certification such as ISO (in terms of ISO/IEC 17025) is encouraged and is considered in the prequalification procedure. If assessment demonstrates that a laboratory meets WHO recommended standards, it is included in the WHO List of Prequalified Quality Control Laboratories that are considered to be acceptable for use by United Nations agencies as well as other interested parties (6).

Once a laboratory is included in the WHO List of Prequalified Quality Control Laboratories, ongoing monitoring of its activities is performed including re-inspections at regular intervals, evaluation of results from participation in an appropriate proficiency testing scheme, and monitoring and investigation of complaints concerning the results of analysis or service provided by the listed laboratories. To facilitate the monitoring each prequalified laboratory is requested to submit a brief annual report on its activities related to quality control of medicines , which should be submitted by the end of March of the following year. An outline of the content of an annual report is published on the WHO web site (7).

A laboratory will be removed from the list if, as a result of re-inspection, it is found that it no longer complies with the specified standards.

Outcomes of the prequalification procedure

As at the end of February 2010, twelve laboratories have been prequalified by the WHO. Five prequalified laboratories are located in the WHO Africa Region, three in Western Pacific Region and one in each of the three regions: Americas, Eastern Mediterranean, Europe and South-East Asia.

Country	Region	Number of PQ laboratories
Algeria	Africa	1
Canada	Americas	1
France	Europe	1
India	South-East Asia	1
Kenya	Africa	2
Morocco	Eastern Mediterranean	1
Singapore	Western Pacific	2
South Africa	Africa	2
Vietnam	Western Pacific	1

Apart from these twelve prequalified laboratories, there are thirty one quality control laboratories participating in the procedure by the end of February 2010. The majority of participating laboratories (32 of 43) are national quality control laboratories.

As part of the capacity building component of the WHO PQ Programme national quality control laboratories participating in the prequalification procedure are, if needed, provided with technical assistance in the form of a pre-audit or 1-3 weeks stay of an expert in the laboratory. WHO PQ also organizes trainings for national quality control laboratories and for laboratories providing testing services to the government in the respective country.

Inspections

An inspection team consists of a WHO PQ inspector based in Geneva and a co-inspector appointed by WHO from a Pharmaceutical Inspection Cooperation Scheme (PIC/S) member inspectorate. An inspector (or inspectors) from the National Drug Regulatory Authority of the country, in which the laboratory is located, is invited to participate as an observer. Pre-qualified laboratories are re-inspected on regular basis, usually every 3 years.

Quality control laboratory inspections were started in March 2004 and up to September 2009, 14 inspections had been performed by WHO.

Non-compliances observed during inspections over the years included the following observations:

- The system of reference substances was insufficient in that:
  - Authorized written standardized operation procedures for handling of reference substances were not available, e.g.:
    - packing of working reference substances
    - labelling of working reference substances
    - acceptance criteria for working substances
  - Inappropriate labelling of working standards
  - Use of reference substances was not documented
- Stocks of reagents and retention samples were not maintained under the appropriate storage conditions
- The training system was insufficient in that:
  - Authorized written standardized operation procedure for training was not available
  - Training was not appropriately documented and assessed
- Authorized written standardized operation procedure for internal audits was not available
- Reagents were not managed properly in that:
  - The labels of some reagents did not specify shelf-life,
  - Certificates of analysis were not available for all reagents
  - Reagents were not properly labelled
- Responsibilities, competencies and functions were not clearly defined in current job descriptions
- The computer software developed by the users were not appropriately validated or verified. Procedures were not established and implemented for protecting the integrity of data
- Authorized written standardized operation procedure for the calibration of critical equipment was not available, for example HPLC, GC, dissolution and disintegration instruments. Equipment calibration and maintenance schedule were not available. Equipment were not regularly qualified, IQ, OQ and PQ protocols/reports were not available
- Validation of microbiological laboratory autoclave was not done in accordance to current guidelines
- Pharmacopoeia test methods were not verified
- Failures to meet specifications ('out of specifications') were not recorded and handled properly

References:

1. http://www.who.int/prequal/info_applicants/eoi/EOI-QCLabsV3.pdf
2. Prequalification of quality control laboratories. Procedure for assessing the acceptability, in principle, of quality control laboratories for use by United Nations agencies. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-first report.* Geneva, World Health Organization, 2007, Annex 5 (WHO Technical Report Series, No. 943) .
   http://www.who.int/prequal/info_general/documents/TRS943/TRS943.pdf#page=111
3. Good Practices for National Pharmaceutical Control Laboratories. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty -sixth report.* Geneva, World Health Organization, 2002, Annex 3 (WHO Technical Report Series, No. 902).
   http://www.who.int/prequal/info_general/documents/TRS902/WHO_TRS_902.pdf#page=37
4. *Quality Assurance of pharmaceuticals. A compendium of guidelines and related materials. Volume 2, Second updated edition. Good manufacturing practices and inspection*. Geneva, World Health Organization, Geneva, 2007.
   http://www.who.int/medicines/areas/quality_safety/quality_assurance/production/en/index.html
5. http://www.who.int/prequal/info_applicants/qclabs/prequal_quality_control_labs.htm

6. http://www.who.int/prequal/lists/PQ_QCLabsList.pdf

http://www.who.int/prequal/info_applicants/qclabs/Annual-Report_Labs.pdf

Thirty-second annual meeting of representatives of national centres participating in the WHO Programme for International Drug Monitoring

2-5 November 2009

There were eight breakout sessions at the annual meeting of pharmacovigilance centres in Rabat, Morocco. Below is a summary of recommendations from these sessions.

Patient safety, including medication errors

This working group looked specifically at improving the yellow card form to facilitate detection of medication errors. The group took the definition of a medication error as "any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is under the control of the health care professional, patient, or consumer".

After reviewing the advantages and limitations of current means of detecting medication errors, the group looked at the yellow card itself. The working group proposed adding the following: frequency of administration, batch number, expiry date, and source. (It was noted that the batch number is not always easy to find; hence the need to include the source of the medicine.). The members also proposed adding: frequency of administration, units (e.g. mg, mcg), and either dose administered or dosage form, comorbidity (other diseases, e.g. renal failure), risk factors (e.g. alcohol, smoking), allergy, and diluent and possible interactions.

Reporting and database needs and practicalities

This working group had looked at the problem of an apparent fall in reporting to UMC from European Union (EU) countries. Eleven European countries submitted no cases to UMC between October 2008 and October 2009. UMC had sent out a questionnaire to 28 European countries to try to establish the reasons for this and to find a solution. The 25 countries that responded had used a variety of ways of submitting data to UMC. Under EU requirements, countries had to submit data on adverse reactions to medicines to the European Medicines Agency (EMEA) via the EudraVigilance network. Some found it extra work to submit data to UMC as well.

The working group recommended that WHO-UMC should be a recipient of data submitted via the EudraVigilance gateway (as requested by 10 EU countries in their responses to the UMC survey since this would require them to submit the data only once). The group said that the EMEA and WHO should collaborate to facilitate this communication technically, bearing in mind national data protection laws. While there was concern that EudraVigilance requires submission of only serious individual case safety reports, as opposed to UMC's VigiBase which requests all reports, the group was informed that this situation would be harmonized through a European Commission legislative proposal (whereby all reports will be required by EudraVigilance as from 2011–2012).

The current UMC requirement of reporting every 90 days was seen to have disadvantages in terms of the high workload every quarter and the delay in signal detection. The working group recommended a reporting interval of 30 days to UMC (though for EU reports, UMC would accept the same timeline as the EMEA). The group also suggested that UMC should send more frequent feedback to national centres to encourage regular reporting (and improved quality of reporting).

In terms of UMC's VigiFlow reporting system, the working group recommended there should be discussion between the EMEA and UMC regarding how to support current and future EU members who are VigiFlow users. In addition, the VigiFlow interface should be translated into more languages, and it was agreed that case narratives may be entered in local languages.

Interaction with academia/regulation

In daily practice many national centres already have drug advisory committees and play a role in education and training. Many contacts – both formal and informal – already take place between pharmacovigilance centres and academia.

Expressing a clear need for pharmacovigilance to be a part of the curriculum of health care professionals, the members of the working group acknowledged that the most practical way of achieving this was to start with a series of lectures and move on to having a fixed module in masters programmes. Examples were given of a pharmacovigilance module in medical school in Senegal and a place in pharmacology training in Ethiopia. There was also felt to be a need to introduce pharmacovigilance at preclinical level.

The working group stated that health professionals need to have a basic knowledge of pharmacovigilance, but that this scientific discipline needs to be made more interesting for them. The working group felt that a strong statement by WHO concerning the need for education would be helpful, and that academia and regulators should cooperate and support each other.

Use of pregnancy and other registers in pharmacovigilance

This working group looked at registers in pharmacovigilance and, where they exist, asked whether they are useful. The group agreed that registers should collect data on the disease, the conditions and specific products, and that they should include information for all patients within a defined area (with a denominator and information on deviations in the group, e.g. a register on congenital malformation). However, before setting up a register it would be necessary to know what data should be collected so that the information available can be used for making useful decisions, especially in the area of medicine surveillance.

Members of the working group felt that registers would be useful for new products about which there is little information. In such cases there could be follow-up with special groups of patients (e.g. the elderly, children, pregnant women) to monitor for long-term side-effects. Pregnancy registers were judged to be useful because few, if any, trials are conducted in pregnant women, and a register is the only way to find out information about the effects of a medicine on pregnant women and the extent of complications.

The working group recommended that guidelines should be provided for the minimum information to be collected in each register so that information can be shared at both national and global levels.

The role of generic manufacturers in pharmacovigilance: old and new issues

There is consensus that generic medicines should be of proven pharmaceutical quality and should have proven equivalence (or bioequivalence) to the originator product. Regulations vary between countries on, for instance, the number of generic suppliers permitted or the inspection of manufacturers or importers before the market launch. A number of concerns were noted, such as the lack of resources for GMP inspections, unclear supply chains that are difficult to control, stability problems in different climates, and the lack of harmonized pharmacopoeia requirements.

Specific pharmacovigilance concerns about generics include pressure to grant a licence because of urgent needs so there is little time to carry out an in-depth assessment of the dossier or evidence, and the fact that generics may contain old substances that have not been reviewed so it is unclear if they are as safe as they should be by current standards. In addition, governments and insurance companies may require the prescription (and use) of generic medicines for cost reasons, yet there remains the question of how and by whom to monitor safety (the manufacterer, a national agency, or within a public health programme).

On the reporting of adverse reactions to medicines of generics, working group members felt that the CIOMS form was widely accepted and there was no need for an additional form, but that guidance was required on the need to report serious adverse reactions, clusters of reactions, and medication errors that result in injury. There should be rules, the working group said, that make responsibilities very clear (for the manufacturer, pharmacist, physician, nurse etc). Companies should have a pharmacovigilance system in place, they should notify changes of suppliers or vendors, and in case of safety concerns regulators should have the right to request post-authorization safety studies (PASS).

The working group said there should be guidance on risk management plans and their implementation. It would be important to have prequalification lists of manufacturers, vendors and suppliers, lists of risk management plans, and medicine master files. From the EU, periodic safety update reports (PSURs) could be useful (available at http://www.emea.europa.eu/).

Mobilizing resources for pharmacovigilance

A recent survey of pharmacovigilance activities in 55 low-income and middle-income countries identified lack of resources as one of the major challenges facing pharmacovigilance centres in these countries. The working group suggested that, when a country is admitted to the WHO Programme for International Drug Monitoring, it should be informed not only of the need to have a certain number of reports but also the need to advocate for budgetary allocations.

Sustainability of pharmacovigilance requires a structured training programme which will necessitate introducing a pharmacovigilance curriculum into the training programmes of health care professionals and setting up a career progression scheme for pharmacovigilance practitioners, the working group said. The members further stressed the need for both social marketing and high-level advocacy, and emphasized that each national centre should draw up a clearly articulated plan with evaluation indicators. They proposed integrating pharmacovigilance into regional and subregional networks and setting up a web site to share ideas for (and experiences of) success.

Funds that could be tapped include those allocated for pharmacovigilance in public health programmes (which are often underutilized). Pharmacovigilance centres could set aside a certain amount of funds from the registration of medicines for monitoring of such medicines, or charging a retainer fee for re-registration (though this was not successful in Europe), or by generating resources through pharmacovigilance services.

The working group proposed a list of "actionable points" for resource mobilization, such as presenting pharmacovigilance as a public health emergency, showing that monitoring safety is cost-effective, and incorporating pharmacovigilance into all public health programmes. It was proposed that WHO and UMC should lead global collaboration in resource mobilization and that the meeting of national centres should set up an informal committee to develop advocacy and promotional materials for the social marketing of pharmacovigilance.

Pharmacovigilance for medicines in neglected diseases

The working group decided that any discussion of this topic must start with the assumption that neglected diseases are a global problem and should be tackled accordingly. The group focused specifically on large-scale infectious diseases which seem to be spreading and affecting more people. The reasons for this include the decreased efficacy of existing therapies (resistance), low compliance with medicines for chronic diseases, and the decreased efficacy of insecticides used to control vectors. For the pharmaceutical industry, it is necessary to have a market that will be profitable and for investments in intellectual property to be secure.

Some of the major neglected diseases are in countries with limited pharmacovigilance capacity and limited resources. Therefore much depends on the approach of the government. Some may control the manufacture, treatment and supply of medicines for large-scale infectious diseases and implement specialized pharmacovigilance tools (as in the case of Brazil with HIV medicines, benznidazole and thalidomide), while others may rely on the market to supply the medicines people need. In many cases there are difficulties in treating neglected diseases due to lack of available treatments, absence of real-time evaluation and pharmacovigilance measures, and the problem of counterfeit products.
If there is a developed system of pharmacovigilance, then risk minimization measures are normally effective, but in other countries specific disease programmes (e.g. HIV in Brazil, malaria in Ghana) may include the pharmacovigilance functions. Some countries collaborate with NGOs to try to implement safety monitoring measures.

Vaccines

In discussing vaccines and pharmacovigilance, this working group recommended that staff of national pharmacovigilance centres should be trained to identify adverse events following immunization (AEFIs). The working group also suggested that guidelines should be developed to assist national centre staff in reporting of AEFIs. Identifying a need for early education on vaccine safety, the group proposed that member countries should introduce vaccine surveillance activities into their medical school curricula.

Because of the lack of resources to monitor AEFIs, national centres were encouraged to collaborate with existing programmes (e.g. WHO-EPI, UNICEF programmes). National centres were also asked to provide feedback on any issues (positive or negative) that may result from the collaboration. The working group proposed that the AEFI case definitions from the Brighton Collaboration should be translated into other languages and that a short list of new AEFI terms should be added to the existing WHOART list.

The working group stressed the need for a vaccine dictionary that would include vaccine excipients and dosage contents and recommended that this should be a topic for discussion at the 33rd annual meeting of national centres in 2010.