WHO PHARMACEUTICALS NEWSLETTER

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

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

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This Newsletter is also available on our Internet website:
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No. 2, 2010

A three-year project with the aim to promote safety monitoring of medicines, and in particular to involve consumers in the process, has just been launched. The project which goes under the name Monitoring Medicines has been made possible by a grant from the European Commission. The project involves WHO, the Uppsala Monitoring Centre and many other partners throughout the world.

Read more about this project in a 'Feature article' in this issue of the WHO Newsletter. The Newsletter also includes an article about the WHO Prequalification of Medicines Programme: Inspection of Finished Pharmaceutical Product Manufacturers to increase quality of medicines, as well as the usual sections on Regulatory Matters and Safety of Medicines.

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Regulatory Matters

Safety of Medicines

Feature

Becaplermin

Contraindication recommended

Europe. The European Medicines Agency (EMA) has recommended contraindication for becaplermin (Regranex) in patients with any pre-existing cancer, following a review of the available data at the Agency's Committee for Medicinal Products for Human Use (CHMP) on a possible risk of cancer in patients using the medicine. A similar restriction previously applied, but only for patients who had a skin cancer close to the area where the gel was to be applied. Becaplermin (Regranex) is a gel that is used together with other wound care measures to treat long-term neuropathic skin ulcers in people with diabetes.

The EMEA explains that in an observational study, which compared Regranex-users with a control group of patients who did not use Regranex, the overall risk of developing cancer was not found to be significantly different between Regranex-users and non-users. However, patients who used three or more tubes of becaplermin (Regranex) and who developed cancer had a greater risk to die of their cancer than patients who did not use becaplermin (Regranex). The study had several limitations in its design, including a small number of cases of cancer and is therefore not considered to be robust.

The CHMP noted that becaplermin (Regranex) was modestly effective in treating neuropathic ulcers in patients with diabetes, but that its long-term effectiveness (over 20 weeks) had not been proven. The Committee also noted that while there was no firm evidence of a link between becaplermin (Regranex) and cancer, there was also not enough evidence to rule out such a link. Therefore, the CHMP concluded that the benefits of becaplermin (Regranex) continue to outweigh its risks, but that, as a precautionary measure, the gel must not be used in patients with any pre-existing cancer. In addition, the manufacturer has been asked to conduct more research to investigate the way the medicine is absorbed by the body and its potential risks.

Reports in WHO Global ICSR database, Vigibase:

Becaplermin

Number of reports: 343

Most reported reactions (number of events):

Condition aggravated:	*31*
Pain:	*45*
Death:	*23*
Therapeutic response decreased:	*33*
Paraesthesia:	*29*
Skin hypertrophy:	*55*
Infection:	*25*
Skin disorder:	*36*
Rash etythematous:	*21*

(See WHO Pharmaceuticals Newsletter No.3, 2008 for a boxed warning about increased cancer risk in the USA.)

Reference:
Press Release, Questions and answers, EMEA, 18 February 2010 (www.emea.europa.eu).

Clopidogrel

Boxed Warning about reduced effectiveness in certain patients

USA. The US Food and Drug Administration (US FDA) notified health-care professionals and patients that a Boxed Warning has been added to the prescribing information for clopidogrel (Plavix). The Boxed Warning is about patients who do not effectively convert clopidogrel (Plavix) to its active form in the body (poor metabolizers) because of low CYP 2C19 activity. Clopidogrel (Plavix) is an anti-blood clotting medicine that is used to reduce the risk of heart attack, unstable angina, stroke, and cardiovascular death in patients with cardiovascular disease.

The Boxed Warning in the drug label will include the following information:

- to warn about reduced effectiveness in patients who are poor metabolizers of clopidogrel (Plavix).
- to inform health-care professionals that tests are available to identify genetic differences in CYP2C19 function.
- to advise health-care professionals to consider use of other anti-platelet medications or alternative dosing strategies for clopidogrel (Plavix) in patients identified as poor metabolizers.

The US FDA also advises that although a higher dose regimen (600 mg loading dose followed by 150 mg once daily) in poor metabolizers increases antiplatelet response, an appropriate dose regimen for poor metabolizers has not been established in a clinical outcome trial.

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

Clopidogrel and proton-pump inhibitors

Updates on warning about interaction

Europe (1). The EMA recommended to update the

existing warning over the concomitant use of clopidogrel-containing medicines and proton-pump inhibitors (PPIs). In May 2009, the Agency's Committee for Medicinal Products for Human Use (CHMP) recommended that the product information for all clopidogrel-containing medicines be amended to discourage the concomitant use of PPIs and clopidogrel unless absolutely necessary. The EMA states that two recent studies, completed at the end of August 2009, confirmed that omeprazole can reduce the levels of the active form of clopidogrel in the blood and reduce its anti-platelet effects, therefore supporting the conclusion that there is an interaction between clopidogrel and omeprazole and esomeprazole. Based on the currently available data, the CHMP have concluded that there are no solid grounds to extend the warning to other PPIs. Therefore, the class warning for all PPIs has been replaced with a warning stating that only the concomitant use of clopidogrel and omeprazole or esomeprazole should be discouraged.

New Zealand (2). New Zealand Medicines and Medical Devices Safety Authority (Medsafe) has advised that an interaction between clopidogrel and omeprazole has been confirmed following two pharmacokinetic/pharmacodynamic interaction studies. The results from these studies indicate that co-administration of clopidogrel with omeprazole results in significantly reduced exposure to the active metabolite of clopidogrel. Clopidogrel is a pro-drug that is converted to its active form by CYP3A4 and 3A5, with contributions from CYP2C19, CYP2C9, and CYP1A2. Omeprazole is an inhibitor of CYP2C19.

According to Prescriber Update, in the first randomized crossover study where clopidogrel and omeprazole were administered at the same time, reductions of 42% and 40% were observed in maximum plasma concentration (Cmax) and exposure (Area Under the Curve, AUC0-24) to the active metabolite of clopidogrel, respectively. In the second crossover study where clopidogrel and omeprazole were given 12 hours apart, findings were similar to those in the first study, indicating that administering clopidogrel and omeprazole at different times does not prevent this interaction.

Health-care professionals are advised to avoid the concomitant use of clopidogrel with omeprazole and other CYP2C19 inhibitors e.g. esomeprazole, cimetidine, fluconazole, ketoconazole, viriconazole, etravirine, fluoxetine, and fluvoxamine. The New Zealand data sheets for clopidogrel will be updated to include information to avoid concomitant use with omeprazole and other CYP2C19 inhibitors

(See WHO Pharmaceuticals Newsletters No. 2, No. 3, No. 4 and No.5, 2009 for information on the possible interaction between clopidogrel and proton pump inhibitors in the USA, Ireland, Europe, Canada and New Zealand).

***References**:*
(1). Public statement, EMEA 17 March 2010 (www.emea.europa.eu).
(2). Prescriber Update Vol. 31, No.1 February 2010 (www.medsafe.govt.nz).

Deferasirox

New Boxed Warning

USA. Novartis Oncology and the US FDA notified health-care professionals about recent changes in the prescribing information (PI) for deferasirox (Exjade). The medicine is indicated for the treatment of chronic iron overload due to blood transfusions in patients 2 years of age and older. A Boxed Warning was added to the PI, stating that deferasirox (Exjade) may cause:

- renal impairment, including failure.
- hepatic impairment, including failure.
- gastrointestinal hemorrhage.

In some reported cases, these reactions were fatal. These reactions were more frequently observed in patients with advanced age, high risk myelodysplastic syndromes, underlying renal or hepatic impairment or low platelet counts. Exjade therapy requires close patient monitoring, including measurement of serum creatinine and/or creatinine clearance as specified in the PI and serum transaminases and bilirubin as specified in the PI.

New language was also added to the Contraindications, Warnings and Precautions, and Drug Interactions sections of the product information.

Reports in WHO Global ICSR database, Vigibase:

Deferasirox

Number of reports with liver and biliary system disorders and neoplasm: 133
Number of reports with urinary system disorders: 147
Number of reports with haemorrhage: 38

Most reported reactions (number of events):
Hepatic enzymes increased: 56
Hepatic failure: 27
Hepatic function abnormal: 54

Renal failure acute: 51
Renal failure chronic: 39

Renal function abnormal: 41
Renal tubular disorder: 10
Gastrointestinal haemorrhage: 21
Haemorrhage rectum: 14
Melaena: 12

(See WHO Pharmaceuticals Newsletter No.1, 2010 for potential revisions to prescribing information in Canada and the USA, 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).

***Reference**:*
Safety Information, US FDA 18 February 2010 (www.fda.gov).

Dextropropoxyphene

Risk-benefit balance unfavourable

New Zealand. The New Zealand Medicines and Medical Devices Safety Authority (Medsafe) has announced that it is currently implementing the recommendations by the Medicines Adverse Reactions Committee (MARC) that consent to distribute dextropropoxyphene-containing medicines be revoked. In the meantime, Medsafe advises prescribers not to start any new patients on dextropropoxyphene-containing medicines and to start reviewing the analgesic requirements of patients currently taking these medicines.

The MARC concluded the following.

- Efficacy studies had demonstrated that dextropropoxyphene-containing medicines were no better than paracetamol used at the maximum recommended dose.
- The available data on adverse reactions showed that these medicines have the potential to cause more adverse reactions than paracetamol used at recommended doses.
- These medicines are more dangerous than other analgesics in overdose.
- Overall the benefits of these medicines do not outweigh the risks associated with their use.

(See WHO Pharmaceuticals Newsletter No. 4, 2009 for recommendation to withdraw the marketing authorizations for dextropropoxyohene-containing medicines in Europe).

***Reference**:*
Prescriber Update Vol. 31, No.1 February 2010 (www.medsafe.govt.nz).

Didanosine

Risk of non-cirrhotic portal hypertension

USA. The U.S. FDA has alerted health-care professionals and patients about non-cirrhotic portal hypertension in patients using didanosine (Videx or Videx EC). Didanosine is used to treat human immunodeficiency virus (HIV) infection. The US FDA has received 42 post-marketing cases of non-cirrhotic portal hypertension in patients using didanosine with 4 deaths in those reported cases. The Agency explains that the cause of death in the four patients was due to: hemorrhage from esophageal varices in two patients; progressive liver failure in one patient; and a combination of multi-organ failure, cerebral hemorrhage, sepsis, and lactic acidosis in one patient.

Based on the number of well-documented cases and exclusion of other causes of portal hypertension such as alcohol-related cirrhosis or hepatitis C, the US FDA has concluded that there is an association between use of didanosine and development of non-cirrhotic portal hypertension. Because of the potential severity of portal hypertension, the Agency has revised the Warning and Precautions section of the didanosine label to include information about non-cirrhotic portal hypertension. Didanosine already has a Boxed Warning for lactic acidosis and hepatomegaly with steatosis.

The US FDA states that the clinical benefits of didanosine for certain patients with HIV continue to outweigh its potential risks. The decision to use this medicine, however, must be made on an individual basis between the treating physician and the patient.

Reports in WHO Global ICSR database, Vigibase:

Didanosine

Number of reports with cardiovascular disorders, general: 134

Most reported reactions (number of events):
Hypertension portal: 25
Cardiac failure: 26
Hypertension: 23
Hypotension: 34

Reference:
Safety Information, US FDA 29 January 2010 (www.fda.gov).

Erythropoiesis-stimulating agents

Risk management programme required

USA. The US FDA has notified health-care professionals and patients that all Erythropoiesis-stimulating agents (ESAs) must be used under a risk management programme, called a risk evaluation and mitigation strategy (REMS). The Agency has required a REMS because studies show that ESAs can increase the risk of tumor growth and shorten survival in patients with cancer (breast, non-small cell lung, head and neck, lymphoid, and cervical cancer) who use these products. Studies also show that ESAs can increase the risk of heart attack, heart failure, stroke or blood clots in patients who use these drugs for other conditions. ESAs are approved for the treatment of anemia resulting from chronic kidney failure, chemotherapy, certain treatments for Human Immunodeficiency Virus (HIV), and also to reduce the number of blood transfusions during and after certain major surgeries.

As part of the REMS, a Medication Guide explaining the risks and benefits of ESAs must be provided to all patients receiving an ESA. In addition to the Medication Guide, the manufacturer of the products (Amgen) was required to develop the ESA APPRISE (Assisting Providers and Cancer Patients with Risk Information for the Safe use of ESAs) Oncology program for health-care professionals who prescribe ESAs to patients with cancer. Under this programme, the company will ensure that only those hospitals and health-care professionals who have enrolled and completed training in the program will prescribe and dispense ESAs to patients with cancer

Reference:
Safety Information, US FDA 16 February 2010 (www.fda.gov).

Human immune globulin

Risk of intravascular haemolysis

Canada and USA. Cangene Corporation, Baxter Healthcare Corporation, Health Canada and the US FDA notified health-care professionals that cases of intravascular hemolysis (IVH) and its complications, including fatalities, have been reported in patients treated for immune thrombocytopenic purpura (ITP) with Rho(D) immune globulin intravenous (human) (WinRho® SDF), which is a gamma globulin (IgG) fraction containing antibodies to the Rho(D) antigen. Fatal outcomes associated with IVH and its complications have occurred most frequently in patients aged over 65 with co-morbid conditions.

The Boxed Warning informs health-care professionals of the following.
- IVH can lead to clinically compromising anemia and multi-system organ failure including acute respiratory distress syndrome.
- Serious complications including severe anemia, acute renal insufficiency, renal failure and disseminated intravascular coagulation have also been reported.
- Patients should be closely monitored in a health care setting for at least eight hours after administration.
- A dipstick urinalysis should be performed at baseline, 2 hours, 4 hours after administration and prior to the end of the monitoring period.
- Patients should be alerted to and monitor for signs and symptoms of IVH, including back pain, shaking chills, fever, and discoloured urine or hematuria. Absence of these signs and/or symptoms of IVH within eight hours do not indicate that IVH cannot occur subsequently.
- If signs and/or symptoms of IVH are present or if IVH is suspected after the administration of the medicine, post-treatment laboratory tests should be performed including plasma haemoglobin, urinalysis, haptoglobin, LDH and plasma bilirubin (direct and indirect).

The new contraindications have been added, stating that WinRho® SDF should not be administered to ITP patients:
- with ITP secondary to other conditions including leukemia, lymphoma, or active viral infections with EBV (Epstein-Barr virus) or HCV (hepatitis C)
- who are elderly with co-morbidities predisposing to acute hemolytic reaction (AHR) or its complications
- with evidence of autoimmune hemolytic anemia (Evan's Syndrome), or Systemic Lupus Erythematosus (SLE) or anti phospholipid antibody syndrome (APS)
- who are IgA deficient.

Physicians are advised that if a patient has evidence of hemolysis (reticulocytosis greater than 3%) prior to ITP treatment, or is at high risk for hemolysis (positive DAT not attributed to previous immune globulin administration), alternate therapies must be used.

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

***Reference**:*
Advisories, Warnings and Recalls, Health Canada 22 March 2010 (www.hc-sc.gc.ca).
Safety Information, US FDA 10 March 2010 (www.fda.gov).

Isotretinoin

Association with severe skin reactions

Canada. Health-care professionals have been notified that there have been very rare post-marketing reports of severe skin reactions (e.g. erythema multiforme, Stevens-Johnson syndrome, and toxic epidermal necrolysis) associated with use of isotretinoin (ACCUTANE). Isotretinoin (ACCUTANE) is a retinoid that is indicated for the treatment of severe nodular and/or inflammatory acne, acne conglobata and recalcitrant acne. Prescribers are also advised that patients should be monitored closely for severe skin reactions and discontinuation of isotretinoin (ACCUTANE) should be considered if warranted. The Canadian Product Monograph will be updated with this safety information.

According to the letter issued by Hoffmann-La Roche Limited for heal-care professionals, based on a review of the company's safety database (as of 6 November 6 2009), 66 cases of severe skin reactions in adults and children have been reported worldwide in association with isotretinoin (ACCUTANE). Two of the cases were fatal. While there are confounding factors for the majority of the reports received, a causal association between the medicine and those severe skin reactions cannot be excluded

(See WHO Pharmaceuticals Newsletter No. 4, 2005 for risk management programme in the USA)

Reference:
Advisories, Warnings and Recalls, Health Canada 16 February 2010 (www.hc-sc.gc.ca).

Long-acting beta-agonists

New safety requirements

USA. The US FDA notified health-care professionals and consumers that it is requiring a risk management strategy (REMS) and class-labeling changes for all Long-Acting Beta-Agonists (LABAs). The REMS will require a revised Medication Guide written specifically for patients, and a plan to educate health-care professionals about the appropriate use of LABAs. These changes are based on the analyses by the Agency of studies showing an increased risk of severe exacerbation of asthma symptoms, leading to hospitalizations in pediatric and adult patients as well as death in some patients using LABAs for the treatment of asthma. LABAs are approved as single-ingredient products and as an ingredient in combination products containing inhaled corticosteroids for the treatment of asthma and chronic obstructive pulmonary disease (COPD).

Health-care professionals are reminded of the following.
- The use of LABAs is contraindicated without the use of an asthma controller medication such as an inhaled corticosteroid. Single-ingredient LABAs should only be used in combination with an asthma controller medication; they should not be used alone.
- LABAs should only be used long-term in patients whose asthma cannot be adequately controlled on asthma controller medications.
- LABAs should be used for the shortest duration of time required to achieve control of asthma symptoms and discontinued, if possible, once asthma control is achieved. Patients should then be maintained on an asthma controller medication.

- Pediatric and adolescent patients who require the addition of a LABA to an inhaled corticosteroid should use a combination product containing both an inhaled corticosteroid and a LABA, to ensure compliance with both medications.
- LABAs should not be started in patients with acutely deteriorating asthma.
- LABAs do not relieve sudden-onset asthma symptoms. A rescue inhaler, such as an albuterol inhaler, should be prescribed to treat sudden asthma symptoms.

The US FDA states that the benefits of LABAs in improving asthma symptoms outweigh the potential risks when used appropriately with an asthma controller medication in patients who need the addition of LABAs. The US FDA also says that there are insufficient data to conclude whether using LABAs with an inhaled corticosteroid reduces or eliminates the risk of asthma-related death and hospitalizations. The Agency is requiring the manufacturers of LABAs to conduct studies evaluating the safety of LABAs when used in conjunction with an inhaled corticosteroid.

Reference:
Safety Information, US FDA 18 February 2010 (www.fda.gov).

Natalizumab

Update on the risk of progressive multifocal leukoencephalopathy and immune reconstitution inflammatory syndrome

UK (1). The Medicines and Healthcare products Regulatory Agency (MHRA) has warned that the risk of developing progressive multifocal leukoencephalopathy (PML) with natalizumab increases after two years of therapy. Natalizumab (Tysabri) is a disease-modifying therapy for patients with multiple sclerosis who have high disease activity despite treatment with beta-interferon, or who have rapidly evolving severe relapsing remitting disease. The Agency advises that patients with multiple sclerosis should be informed of the risk before treatment, and again after two years. The risk of developing PML beyond three years of treatment is currently unknown. Natalizumab should be promptly discontinued if PML is suspected, with subsequent appropriate evaluation including a standardised MRI scan and lumbar puncture.

According to the Drug Safety Update, up to 20 January 2010, 31 cases of PML have been reported worldwide in patients with multiple sclerosis receiving natalizumab, eight of which were fatal. Approximately 66 000 people have been exposed worldwide to natalizumab up to 20 January 2010. Out of the 31 confirmed cases, 23 cases occurred in patients exposed to natalizumab for two years or more. The reporting rate is equivalent to around one to two cases of PML for every 1000 patients treated with natalizumab (Tysabri) for two or more years.

The MHRA also warns that use of plasma exchange/immunoadsorption accelerates the development of immune reconstitution inflammatory syndrome (IRIS) in the following days to weeks. Plasma exchange/ immunoadsorption has often been used to reduce natalizumab levels more quickly when PML has been identified. Health-care professionals are advised that patients treated for PML should be closely monitored for the development of IRIS. Those with signs and symptoms suggestive of IRIS should receive intensive care monitoring.

Product information for healthcare professionals and patients is being updated with the above information.

USA (2). The US FDA has alerted health-care professionals and patients that the risk of developing PML increases with the number of natalizumab (Tysabri) infusions received. This new safety information will be included in the natalizumab (Tysabri) drug label and Medication Guide.

Natalizumab (Tysabri) is approved for the treatment of relapsing forms of multiple sclerosis as well as for treating moderately to severely active Crohn disease. Natalizumab (Tysabri) is administered as a single intravenous infusion every four weeks. In the United States, natalizumab (Tysabri) has only been available through a risk minimization plan called Tysabri Outreach Unified Commitment to Health (the TOUCH™ Prescribing Program), which is intended to make sure that health-care professionals and patients understand the benefits and potential risks associated with the use of this medicine, including the risk of PML.

According to the Agency, the overall worldwide cumulative rate of PML in patients who have received one or more natalizumab (Tysabri) infusions is 0.5 cases of PML per 1000 patients. Since marketing resumption (July 2006), there have been no cases of PML in patients treated with natalizumab (Tysabri) for less than 12 months. The overall worldwide cumulative rate of PML in patients who have received at least 24 infusions is 1.3 cases of PML per 1000 patients. In the United States, the cumulative rate of PML in patients who have received at least 24 infusions is 0.8 per 1000 patients. Outside of the United States, the cumulative rate of PML in patients who have received at least 24 infusions is 1.9 per 1000 patients. There is limited clinical experience beyond 36 infusions either in clinical trials or in the post-marketing setting.

Information about the occurrence of IRIS in patients who developed PML and subsequently discontinued natalizumab (Tysabri) has also been added to the drug label. The US FDA says that IRIS has been reported in patients who discontinue natalizumab (Tysabri) as a result of developing PML, but not in patients who discontinue the medicine for other reasons. Many patients who stopped natalizumab (Tysabri) due to PML and who received either plasma exchange or immunoadsorption developed IRIS days to several weeks after these treatments.

At this time, based on the available information, the US FDA states that the clinical benefits of natalizumab (Tysabri) continue to outweigh the potential risks.

(See WHO Pharmaceuticals Newsletters No.1, 2010 for recommendations of new measures to minimize the risk of PML in Europe as well as No. 5, 2009 and No. 4, 2006 for reports of PML and the risk management programme for natalizumab in the USA.)

References:

(1) Drug Safety Update, MHRA Volume 3, Issue 8, March 2010 (www.mhra.gov.uk).
(2) Safety Information, US FDA 5 February 2010 (www.fda.gov).

Cough and cold medicines

Clarification about the use of antihistamines in children

New Zealand. Medsafe advised heath-care professionals about the use of antihistamines in children in relation to the recommendation issued in 2009 that oral cough and cold medicines, with the exception of those containing only bromhexine, be contraindicated in children under six years of age.

The advice include the following.
• The Cough and Cold Review Group (CCRG) concluded that there was no evidence to support the efficacy of antihistamines in treating the symptoms of the common cold in children. As the risk-benefit balance is unfavourable, medicines containing antihistamines should not be used in children under six years of age for this indication.
• The use of antihistamines in children for the treatment of allergic conditions was not considered by the CCRG and is therefore not affected by the recommendations of the CCRG.

(See WHO Pharmaceuticals Newsletters No.6, 2009 &No. 1, 2010 for recommendation of contraindication in New Zealand, as well as No. 2 and 3, 2009 for 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. 31, No.1 February 2010 (www.medsafe.govt.nz).

Fluoxetine

Possible small increased risk of congenital cardiac defects

UK. Based on the meta analysis of recent epidemiological data, the MHRA advised that a possible small increased risk of congenital cardiac defects in association with fluoxetine in early pregnancy, and that the risk of congenital cardiac defects for fluoxetine is similar to that for paroxetine. Fluoxetine is an antidepressant of the selective serotonin reuptake inhibitor (SSRI) class. The MHRA explains that the cardiac defects reported in the studies included in the meta analysis for fluoxetine were varied, and ranged in severity from reversible ventricular septal defects to transposition of the great vessels.

Health-care professionals are also advised that there are insufficient data to draw conclusions on whether there is a risk of congenital anomalies for other SSRIs, but the possibility of a class effect cannot be excluded. The potential risks should be considered in the context of the benefits of treating depression in pregnancy.

The MHRA states that the current Summary of Product Characteristics and Patient Information Leaflets are being revised to reflect this information for fluoxetine-containing products.

Reference:
Drug Safety Update, MHRA, Volume 3, Issue 8, March 2010 (www.mhra.gov.uk)

H1N1 pandemic vaccines

Reports of suspected adverse reactions

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

According to the fourteenth weekly update, as of 14 March 2010, at least 42.3 million people, including at least 488 000 pregnant women, had been vaccinated with one of the three centrally authorised vaccines marketed in the European Economic Area (Celvapan, Focetria or Pandemrix). (Arepanrix is not marketed in the EEA). As of 14 March 2010, a total of 14 015 case reports (518 reports for Celvapan, 2947 reports for Focetria, 10 574 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 14 March 2010, a total of 1058 reports worldwide were received by EudraVigilance.

The vast majority of the adverse reactions that had been reported as of 14 March 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.

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

Ireland (2). 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 18 March 2010 update, it is estimated that approximately 1.6 million doses have been distributed and over 900 000 doses have been administered in Ireland. Up to 16 March 2010, the IMB received 1606 reports of suspected adverse reactions to the two Pandemic H1N1 vaccines (1110 adverse reaction reports for Pandemrix, 472 reports for Celvapan, brand unknown in 24 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 caregivers to monitor the temperature of young children following vaccination.

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

Switzerland (3). The Swiss Agency for Therapeutic Products (Swissmedic) updates information on reports of suspected adverse events following vaccination with pandemic influenza vaccines. According to the 18 February 2010 update, as of 12 February, 286,240 doses of Focetria®, 1,000,540 doses of Celtura®, and 1,662,470 doses of Pandemrix® have been delivered. It is estimated that 14 to 20% of the Swiss population (the midlevel in this range is about 1.3 million people) were administered the vaccines. Up to 12 February, there have been 524 reports (55 reports for Focetria®, 30 reports for Celtura® and 439 reports for Pandemrix®). The majority of adverse events reports are self-limited reactions at the injection site, as well as generalized reactions such as headache, fever, muscle aches and joint pain.

Swissmedic comments 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, EMA (www.emea.europa.eu).
(2) Update on National Monitoring Experience with Pandemic H1N1 Vaccines, IMB (www.imb.ie)
(3) Latest information about vigilance for H1N1 flu vaccines in Switzerland, Swissmedic, (www.swissmedic.ch).

Saquinavir

Possible association with abnormal heart rhythms

USA. The US FDA notified health-care professionals and patients that it is reviewing clinical trial data suggesting that saquinavir (Invirasein) in combination with ritonavir (Norvir) may cause prolongation of the QT and PR intervals. Prolongation of the QT interval may lead to torsades de pointes. Prolongation of the PR interval may also lead to heart block. Saquinavir (Invirase) is an antiretroviral medication that is used in combination with ritonavir (Norvir) and other antiretroviral medicines to treat HIV infection in adults.

The US FDA explains that the preliminary data submitted by the manufacturer show that when saquinavir (Invirasein) boosted with ritonavir (Norvir) (1000mg/100mg) was given to healthy patients aged 18 to 55 years old, there was a dose-dependent prolongation of the QT and PR intervals. The magnitude of the effect and clinical implications of QT and PR interval prolongation are still being reviewed by the Agency.

Health-care professionals are advised to be aware of this potential risk for changes to the electrical activity of the heart. Saquinavir (Invirasein) and ritonavir (Norvir) should not be used in patients already taking medications known to cause QT interval prolongation such as Class IA (such as quinidine) or Class III (such as amiodarone) antiarrhythmic drugs, or in patients with a history of QT interval prolongation, preexisting conduction system disease, ischemic heart disease, cardiomyopathy, or underlying structural heart disease.

Reference*:*

Safety Information, US FDA 23 February 2010 (www.fda.gov).

Seasonal flu vaccine

Summary of spontaneous reports

New Zealand. Medsafe issued an overview of all the adverse events following immunization (AEFIs) reported to the Centre for Adverse Reactions Monitoring (CARM) associated with the seasonal flu vaccine in previous years. This includes 1509 reports from1965 to the end of September 2009. Details

of the reported AEFIs are available in the Prescriber Update (http://www.medsafe.govt.nz/profs/PUArticles/PDF/PrescriberUpdate_feb10_WEB.pdf).
It states that a review of the reported AEFI by CARM and Medsafe has not altered the benefit risk balance for these vaccines which continues to be favourable.

Reference:
Vol. 31, No.1 February 2010 (www.medsafe.govt.nz)

Serotonergic agents

Discontinuation syndrome

New Zealand. Prescribers are reminded that discontinuation syndrome can occur following the abrupt cessation of serotonergic medicines such as selective serotonin reuptake inhibitors (SSRIs). To reduce the likelihood of discontinuation syndrome, the dose of serotonergic agents should be reduced gradually over a period of several weeks or months. According to the Prescriber Update, paroxetine and venlafaxine have been associated with discontinuation syndrome more often than the other serotonergic antidepressants. Common symptoms associated with discontinuation syndrome include dizziness, paraesthesia, headache, anxiety, agitation, tremor, sweating, confusion and nausea. Symptoms can occur within a few days of discontinuation or may be delayed, particularly in the case of fluoxetine, due to its longer half life.

Reference:
Prescriber Update Vol. 31, No.1 February 2010 (www.medsafe.govt.nz).

Simvastatin

Increased risk of muscle injury with high doses

USA. The US FDA warned health-care professionals and patients that there is an increased risk of myopathy in patients taking the highest approved 80 mg dose of simvastatin (cholesterol-lowering medicine), compared to patients taking lower doses of simvastatin and possibly other statin medications. The most serious form of myopathy is rhabdomyolysis.
Rhabdomyolysis is a rare adverse event reported with all statins. The risk of myopathy is also increased when simvastatin, especially at the higher doses, is used with certain drugs. The Agency recommends dose limitations of simvastatin as follows, due to the potential drug-drug interactions.

Do not use simvastatin with these medications:
- Itraconazole
- Ketoconazole
- Erythromycin
- Clarithromycin
- Telithromycin
- HIV protease inhibitors
- Nefazodone

Do not use more than 10mg of simvastatin with these medications:
- Gemfibrozil
- Cyclosporine
- Danazol

Do not use more than 20mg of simvastatin with these medications:
- Amiodarone
- Verapamil

Do not use more than 40mg of simvastatin with this medication:
- Diltiazem

Myopathy and rhabdomyolysis are listed as possible side effects in the simvastatin and other statin drug labels. Known risk factors for developing rhabdomyolysis include age (> 65 years), low thyroid hormone levels (hypothyroidism), and poor kidney function.

The above notification has come from the US FDA's review of data from the clinical trial called the Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine (SEARCH) trial, and other sources. The SEARCH trial evaluated over 6.7 years the number of major cardiovascular events (heart attack, revascularization, and cardiovascular death) in 6031 patients taking 80 mg of simvastatin compared to 6033 patients taking 20 mg of simvastatin. All patients in the study had previously had a heart attack. According to the Agency, preliminary results showed that more patients in the simvastatin 80 mg group developed myopathy compared to patients in the simvastatin 20 mg group (52 [0.9%] cases compared to 1 case [0.02%]). Moreover, 11 (0.02%) of the patients in the simvastatin 80 mg group developed rhabdomyolysis compared to no patients in the simvastatin 20 mg group.

(See WHO Pharmaceuticals Newsletter No.4, 2008 for increased risk of rhabdomyolysis with combination of simvastatin and amiodarone in the USA).

***Reference**:*
Safety Information, US FDA 19 March 2010 (www.fda.gov).

Photosensitivity reactions

New Zealand. Medsafe reminded health-care professionals of the risk of photosensitivity reactions with a number of topical and systemic medicines. The Prescriber Update indicates the ten most commonly reported medicines associated with photosensitivity reactions in New Zealand. They are 1. doxycycline, 2. hydrochlorothiazide, 3. amiodarone, 4. piroxicam, 5. chlorpromazine, 6. trimethoprim/sulfamethoxazole (co-trimoxazole), 7. captopril, 8. enalapril, 9. bendroflumethiazide, 10. carbamazepine. Photosensitivity reactions typically appear as unexpected sunburn or a dry or blistering rash on sun-exposed skin. The most commonly affected areas are the face, neck, arms, backs of hands, and often lower legs and feet.

Health-care professionals are advised to identify the photosensitising agent and withdraw it if possible. Patients are recommended to take the sun protection measures when using a medicine which has been associated with photosensitivity reactions, such as covering up with closely-woven clothing.

Reference:
Prescriber Update Vol. 31, No.1 February 2010 (www.medsafe.govt.nz).

New international collaboration for safer use of medicines and better patient care

A major international project, with the full name 'Optimizing drug safety monitoring to enhance patient safety and achieve better health outcomes' has recently been launched.

The project, with the short name 'Monitoring Medicines', is funded by the European Commission (Seventh Framework Programme (FP-7) of the Research Directorate), and is aiming to improve patient safety both within the European Union (EU) and in other regions. The project will run for 3 ½ years. Partners in the project cover a wide range of organizations dedicated to improving public health through safer use of medicines. The project was developed by WHO and will be coordinated by the WHO Collaborating Centre, the Uppsala Monitoring Centre (UMC) with WHO as the main partner.

Other partners in the project are:

- Copenhagen HIV Programme, Denmark
- University of Ghana Medical School, Ghana
- Pharmacy and Poisons Board, Kenya
- Centre Anti Poison et de Pharmacovigilance du Maroc, Morocco
- Lareb, Netherlands Pharmacovigilance Centre, Netherlands
- Zuellig Family Foundation, the Philippines
- Medical Products Agency, Sweden
- Elliot Brown Consulting Limited, United Kingdom
- National Patient Safety Agency, United Kingdom

Concepts and objectives

Throughout the world, medicines represent one of the most common health interventions in patient care. Expenditure on pharmaceuticals ranges from 10–20% of all expenditure on health in the richest countries and from 20–60% in the poorer countries. Over the years our knowledge of appropriate and safe medicines has grown. However, despite substantial progress in our knowledge, the incidence of adverse effects related to medicines and their use remains high. There is a clear and present need to build a network of stakeholders in patient safety, to strengthen information and share the evidence towards actionable learning.

The Monitoring Medicines project will have four "coordination" objectives specifically to:

1. support and strengthen consumer reporting of suspected adverse drug reactions (ADRs)
2. expand the role and scope of national pharmacovigilance centres to identify, analyse and prevent medication errors
3. promote better and broader use of existing pharmacovigilance data for patient safety
4. develop additional methods of pharmacovigilance to complement data from spontaneous reporting systems.

Consumer reporting

Coordination objective 1 has the goal to:

- strengthen consumer reporting of ADRs through review of existing consumer reporting methods,
- identify optimal methods for consumer reporting
- train in best practice in consumer reporting of medication-related problems.

A development in recent years has been the inclusion of patients as reporting partners in the pharmacovigilance networks in some countries in Europe (e.g. Denmark, the Netherlands, Sweden and the United Kingdom). Based on the experience of these countries, guidelines may be developed to help introduce consumer reporting also in other regions.

Through this project, a review of direct consumer reporting practices of suspected ADRs in about ten countries where consumer reporting is already in place, will be carried out. The results of the review will be used to identify and develop optimal methods for consumer reporting. Practical guidelines and tools will be developed for the implementation of these methods; these will then be field-tested in a few countries.

Decrease of medication errors

Coordination objective 2 has the goal to:

Encourage national pharmacovigilance centres to expand their activities to learn more from existing data through:

- collection of information on adverse events relating to drug prescribing, dispensing and administration,
- analysis of these data, and international dissemination of findings.

The World Alliance for Patient Safety has urged WHO Member States to pay the closest possible attention to patient safety. It has requested WHO to establish science-based systems for improving the safety and quality of care.

There are strong reasons for focusing pharmacovigilance more on patient safety; ongoing morbidity and mortality from ADRs, and Adverse Events, remains high and represents a significant burden on health systems. Half of these ADRs are preventable because they have already been identified and documented and/or are known to affect particular population treatment groups.

Thus they indicate a "know - do" gap; that is, the knowledge that an ADR can potentially occur following use of a particular drug is evidently not sufficient to prevent its recurrence. This project will help identify medicines that are frequently associated with safety risks and analyse why the adverse events occurred. By learning from this analysis, preventive measures can be suggested to minimize the recurrence of similar events.

Better use of existing pharmacovigilance data

Coordination objective 3 has the goal to:

Promote better and broader use of existing global pharmacovigilance data through advanced data mining to identify

- medicines with dependence liability and
- medicines of substandard quality.

The focus of this section of the project is to analyse global pharmacovigilance data with advanced data-mining techniques of the UMC.

The 34th meeting of the WHO Expert Committee on Drug Dependence made recommendations for a more scientific basis for using pharmacovigilance data to identify dependence-producing medicines. The research team at UMC will identify indicators of dependence liability, using the ICSR data in the WHO ADR database. The work will take into account previous UMC research where a number of candidate terms reported on known dependence-producing medicines were reviewed for their ability to predict dependence.

The research team at UMC will also use data-mining techniques to analyse more than 100,000 reports in the WHO database that include 'treatment ineffective' as a reporting term. Preliminary investigations suggest that at least some of these reports may be due to substandard and/or counterfeit products.

Possible explanations, other than substandard medicines, will be reviewed. The reports for which therapeutic inefficacy is suggestive of substandard medicines will be further analysed, and resulting patterns reviewed and classified.

Additional methods for pharmacovigilance

Coordination objective 4 has the goal to:

- in collaboration with target countries, develop robust and appropriate pharmacovigilance systems, incorporating both active and passive surveillance methods, to address national drug safety priorities.

Most present-day national pharmacovigilance systems and systems like Eudravigilance and the WHO drug monitoring programme rely solely on "passive'' spontaneous reporting of ADRs. Spontaneous reporting or passive surveillance means that no active measures are taken to find adverse effects other than encouraging health-professionals and others to report safety concerns.

Throughout the world, spontaneous reporting is the most common surveillance method used. It is the easiest to establish and the cheapest to run, but reporting rates are generally very low and subject to strong biases, and there is no knowledge of overall drug use. These problems hinder accurate and timely assessment of risk rates and comparisons between drugs.

Through this project, WHO will advance the development of additional methods such as the Cohort Event Monitoring and other methods of active surveillance, along with the necessary tools and software.

Led by the Copenhagen HIV Programme, the project partner from Denmark, a pilot pharmacovigilance database will be organized by merging ADR data on antiretroviral medicines from several sources, into a common database. A user-friendly web-based query tool will be developed to enable health-care workers to search and retrieve information contained in the database. A web-based distance learning tool to train and assist health-care workers in evaluating the ADR information retrieved, and a risk score calculation tool, to allow evaluation of ADR development based on clinical data, will also be developed.

WHO Prequalification of Medicines Programme: Inspection of Finished Pharmaceutical Product Manufacturers to increase quality of medicines

The quality of medicines supplied in many countries remains a concern. Substandard, counterfeit and adulterated medicines have far-reaching consequences for patients.

Many cases of sub-standard medicines could be prevented through effective implementation of legislation requiring that medicines be produced and controlled in compliance with Good Manufacturing Practices (GMP). The World Health Organization (WHO) defines GMP as "the part of quality assurance that ensures that products are consistently produced and controlled to the quality standards appropriate to their intended use and as required by the marketing authorization". GMP comprises the standards under which the production and control of pharmaceutical products should take place. Specific risk situations associated with the manufacture of pharmaceutical products are cross-contamination and mix-ups[1].

One component of the extensive evaluation process of the United Nations Prequalification of Medicines Programme managed by the WHO focuses on the inspection of facilities manufacturing finished pharmaceutical products. These inspections are performed by teams of inspectors. An inspection team is made up of a WHO inspector plus an appointed inspector from an inspectorate that is a member of the Pharmaceutical Inspection Cooperation Scheme (PIC/S). During inspections, manufacturers are assessed for compliance with WHO GMP. Inspectors further verify the reliability of data submitted in product dossiers against the original data on site[2].

The first inspections were done in June 2001, focusing on manufacturers of HIV/AIDS medicines. Since then, the programme has expanded and now includes products used in the treatment of malaria, tuberculosis, influenza as well as reproductive health products.

During 2008 and 2009, several site inspections were done in China, Egypt, India, Morocco and South Africa. These were mainly sites producing oral solid dosage forms (OSD) - (35 sites). Other sites produced OSD and liquids (6 sites), injections (5 sites) and liquids alone (1 site).

The majority of inspections were done in India (38 out of 47 inspections) focusing on sites producing OSD forms (35/47) used in the treatment of HIV/AIDS. In 2009, four inspections were done at sites producing reproductive health products, and one each at sites producing HIV/AIDS and influenza products, HIV/AIDS and antituberculosis products; and HIV/AIDS, antituberculosis and malaria products.

Co-inspectors were appointed from Australia (5), Switzerland (4), Estonia (5), France (12), Hungary (3), United Kingdom (7), South Africa (2) and Denmark (2). In seven cases of special inspections, sites were inspected by a team of inspectors from WHO without a co-inspector.

There were a small number of major non-compliances in almost all cases. The same sites were not necessarily inspected both years and it is therefore not possible to see any improvement in compliance with GMP.

The number of total and major deficiencies observed in each of the 25 sites inspected in 2009 varied a lot. Some had very few deficiencies totally (around 5), most had 10 - 40 and 5 had more than 40. One site had a total of 100 deficiencies and more than 10 major ones.

Examples of major non-compliances in manufacturing sites of anti-malaria products included lack of validation of processes, insufficient control over deviations, and lack in line clearance procedures with a possibility of mix-ups and a possibility of cross contamination due to inappropriate cleaning. In some manufacturing facilities, sampling and testing was deficient in ensuring the identity of material used in production (including active pharmaceutical ingredients). For sterile products, in some cases, the sterilization process was not validated; aseptic technique and media fill was inadequate and an unacceptable risk of product contamination was identified.

Examples of major non-compliances in manufacturing sites of anti-tuberculosis products included inappropriate management of deviations and changes that may have an impact on product quality. In one site, all deviations inspected showed that when an operator initially reported a deviation, correction of the deviation was completed prior to authorization by the production supervisor, manager, director, and quality assurance. The company further failed to appropriately implement the written programme for ongoing stability testing. Even when there was a backlog in testing stability samples - in some cases up to 90 days delay - the stability laboratory had to assist the quality control laboratory to test finished products for final release.

In one inspection, in several identified cases of Out of Specification (OOS) results, there was no record of the result having been reported by the analysts; and in several cases, no investigation of reported OOS results was performed.

Examples of major non-compliances in manufacturing sites of HIV/AIDS products included insufficient documented evidence that appropriate process validation was done. This was further verified, as there was an inappropriate system for management and control of quality control laboratory generated data. There was lack of traceability of data and source data as the company failed to retain and maintain electronically generated data and results in an accessible form. In several cases, peaks and baselines of chromatograms were essentially similar if not identical, and retention times were identical. There was no electronic source data retained in any way to enable verification of the data.

Examples of major non-compliances in manufacturing sites of reproductive health products included lack of control of changes. In one case, the Change Control procedure appropriately described the process to be followed. However, there were approximately 200 open Change Request forms corresponding to an approximately five-month period. In several cases, there was insufficient air filtration (supply and exhaust) and pressure cascades; inappropriate gowning by operators; and lack of containment to ensure safety of operators, products and protection of the environment. In several cases, room pressures measured were out of specifications. In one case, batches of a product that failed the sterility test were kept on hold for almost a year before being destroyed.

In several inspections of production sites for reproductive health products, the observations were so many that it was not possible to classify the observations into critical, major and minor deficiencies. A higher number of non-compliances were observed at manufacturers of reproductive health products than any other manufacturers.

References

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2. *Prequalification programme. A United Nations programme managed by WHO.* *www.who.int/prequal* *last accessed February 2010.*