This first issue of the Newsletter for the year 2006 covers the usual sections on the safety and regulatory aspects of medicines. The Feature item records the recommendations from the third meeting of the Advisory Committee on Safety of Medicinal Products. As a direct consequence of the discussions at the meeting, the Committee will propose recommendations for safety systems within the HIV/AIDS programme and design an action plan for studies focusing on specific toxicity issues associated with antiretroviral medicine use. The action plan will help deliver effective pharmacovigilance into public health programmes in countries that most need it.

WHO is announcing two new publications: The Handbook for Good Clinical Research Practice (GCP): Guidance for Implementation and, The Safety of Medicines in Public Health Programmes: pharmacovigilance an essential tool. The former will promote global standards for all clinical research studies while the latter will ultimately help each patient receive optimum therapy, and on a population basis, will help ensure the acceptance and effectiveness of public health programmes. Please write to us if you wish additional details or copies of these publications.

We are delighted to note that Portuguese translations of some of the earlier issues of the WHO Pharmaceuticals Newsletter are now available on the ANVISA website, at http://www.anvisa.gov.br/farmacovigilancia/boletim_oms/index.htm. We thank the Brazilian centre, Agência Nacional de Vigilância Sanitária (ANVISA) for taking this initiative in adding to our readership. We look forward to similar efforts from other Member States. We wish you all much happiness and good health in 2006.
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Feature

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**Aleafacept**

**Contraindicated in HIV patients**

**USA.** The United States labelling for aleafacept (Amevive) has been revised to include new safety information, according to a ‘Dear Health-care Provider’ letter issued by Biogen Idec; the revised Contraindications section now states that aleafacept (Amevive) should not be given to patients with HIV infection as it reduces CD4+ T lymphocyte counts that may increase disease complications or accelerate disease progression; the company says that this contraindication is consistent with the company decision not to study the drug in patients with HIV infection and psoriasis over theoretical safety concerns in this population. Other sections of the labelling for aleafacept (Amevive) have also been updated to reflect additional safety information, says Biogen Idec.

**Reference:**
Safety information from the United States Food and Drug Administration, 9 November 2005 (http://www.fda.gov).

**Beta-2 adrenoceptor agonists**

**Label to warn of risk of asthma**

**USA.** The United States Food and Drug Administration (FDA) has requested manufacturers to update the labelling for the long-acting β2-adrenoceptor agonists, salmeterol/fluticasone propionate inhalation powder (Advair Diskus), formoterol inhalation powder (Foradil Aerolizer) and salmeterol inhalation powder (Serevent Diskus), to include new warnings and a Medication Guide to highlight that these drugs may increase the risk of severe asthma episodes and death when these episodes occur. The FDA says that findings from a study showed that there was an increased number of asthma-related deaths in patients receiving a long-acting β2-adrenoceptor agonist in addition to their usual asthma treatment, compared with patients receiving placebo and usual asthma treatment. Information about these risks have been included in the Medication Guide, and will be given to patients when a prescription for long-acting β2-adrenoceptor agonists is refilled or filled, says the Agency. The FDA says that long-acting β2-adrenoceptor agonists should not be the first drug used for asthma treatment, or for worsening or sudden wheezing, and should only be added if asthma is not controlled by other drugs. The FDA advises that patients should always have a short-acting bronchodilator for sudden wheezing, should contact a health-care professional immediately if wheezing worsens while using a long-acting β2-adrenoceptor agonist and should not discontinue long-acting β2-adrenoceptor agonist or asthma treatments unless they have discussed it with their health-care provider. (Also see WHO Pharmaceuticals Newsletter No. 4, 2005 for warnings from Health Canada related to beta-2 agonist bronchodilator use).

**Reference:**

**Clozapine**

**Blood monitoring requirements tightened**

**USA.** Because of a significant risk of agranulocytosis with clozapine and because of the potential for very low absolute neutrophil count (ANC) and agranulocytosis, white blood cell (WBC) count monitoring is essential in patients treated with clozapine. After reviewing recommendations provided by the Pharmacological Drugs Advisory Committee (PDAC) of June 2003, the United States Food and Drug Administration (US FDA) has recommended changes to the current schedule of WBC monitoring for all clozapine users. The new labels will include the following:

- the requirement that the absolute neutrophil count (ANC) should be determined and reported along with each WBC count;
- new parameters for clozapine treatment initiation: WBC > 3500/mm$^3$ and ANC > 2000/mm$^3$;
- need for the initiation of monthly monitoring schedule after one year (six months weekly, six months every two weeks) of WBC counts and ANC in the normal range (WBC ≥ 3500/mm$^3$ and ANC ≥ 2000/mm$^3$);
- addition of cautionary language to prescribers describing the increased risk of agranulocytosis in patients who are rechallenged with clozapine after recovering from an initial episode of moderate leukopenia and that these patients are now required to undergo weekly monitoring for 12 months if they are rechallenged.

In addition, the label will also include a black-box warning on the increased risk of death in elderly patients with dementia-related psychosis who are treated with an atypical antipsychotic. This reflects a class-wide label change.

**Reference:**
Coagulation Factor VII a (Recombinant) Thromboembolic events added to label

USA. Novo Nordisk Inc. has issued a 'Dear Health-care Professional' letter advising that the US labelling for the coagulation Factor VII a (Recombinant) product (NovoSeven) has been updated to include warnings about a possible increased risk of thromboembolic adverse events (AEs), and additional AE information following reports in patients with and without known coagulopathy. Novo Nordisk advises that the revised labelling includes an update to the Warnings section, which states that patients with advanced atherosclerosis, crush injury, disseminated intravascular coagulation or sepsis, or receiving concomitant coagulants, may have an increased risk of developing thrombotic events, and that a study involving elderly non-haemophilia patients with intracerebral haemorrhage indicated that the risk of arterial thromboembolic AEs was potentially increased with the use of Factor VII a recombinant product (NovoSeven). Additionally, the Adverse Reactions section has also been updated with the product (NovoSeven)-related AE reports, including thromboembolic events, and isolated cases of allergy. Novo Nordisk advises that a causal relationship has not been established for the AEs reported.

Reference:

(Kaizen) Ephedrine Hydrochloride tablet Not authorized as a weight-loss product

Canada. Health Canada has advised that misuse of Kaizen Ephedrine HCl tablets has been associated with serious and potentially fatal adverse effects, and warns consumers not to use the oral nasal decongestant for the unauthorized indications of weight loss or increased energy; those who have used Kaizen Ephedrine HCl for these purposes, and experienced adverse effects, are advised to consult their healthcare practitioner. Health Canada says that, although there have been no specific reports associated with Kaizen Ephedrine HCl, there have been reports of adverse events associated with the use of ephedrine in combination with caffeine and other stimulants. According to Health Canada, the distributor has taken action to stop promoting the product for weight loss and as an energy booster.

Reference:

Epoetin products Labels to warn of severe anaemia and pure red cell aplasia

USA. The product labels for epoetin alfa (Epogen, Procrit) and darbepoetin alfa (Aranesp) have been revised following reports of antibody-mediated pure red cell aplasia (PRCA) and severe anaemia associated with erythropoietin agonists. The cases predominantly involved patients with chronic renal failure who received erythropoietin agonist by the subcutaneous route. The Warnings, Adverse Reactions, and Dosage and Administration sections of the labels have been updated accordingly, and include the following safety information: If a patient fails to respond, or has a sudden loss of response, and an anti-erythropoietin antibody-mediated anaemia is suspected, erythropoietin agonists should be withdrawn and the manufacturer contacted to perform assays for binding and neutralizing antibodies. Erythropoietin agonists should be stopped permanently in patients with antibody-mediated anaemia. As antibodies may cross-react, patients should not be switched to other erythropoietin agonists. The IV route of administration is recommended for patients undergoing haemodialysis.

Reference:
'Dear health-care Professional' letters from Amgen and Ortho Biotech, November 2005 (http://www.fda.gov).

Estradiol/testosterone injection Discontinued due to safety reasons

Canada. Sandoz Canada has advised that the estradiol/testosterone (Climacteron) injection has been discontinued because of safety concerns. The company advises that, according to published literature, women with intact uteri receiving testosterone should also receive progestogen concomitantly to prevent endometrial hyperplasia or carcinoma, and that the appropriate progestogen dosage regimen for such women who are receiving estradiol/testosterone is unknown. The company also advises that, according to published literature, estradiol/testosterone (Climacteron) may be associated with hirsutism, aggression and virilisation. Sandoz Canada recommends
that physicians and pharmacists inform users of the discontinuation, and counsel them to visit for re-evaluation and discussion of alternative hormone replacement therapy (HRT). The company says that estradiol/testosterone (Climacteron) supply will continue until stock depletion.


Ketamine
Classified as Class C drug

UK. As of 1 January 2006, Ketamine has become a controlled drug, under the Misuse of Drugs Act. This step has been taken because of its increasing misuse. In the UK it is now a Class C drug, in Schedule 4 part 1, which puts it with the majority of the benzodiazepines such as diazepam etc. However, the drug is not an internationally controlled substance.


Nevirapine
SPC to include new hepatotoxic warnings

UK. The Summary of Product Characteristics (SPC) for nevirapine (Viramune) has been updated with new hepatotoxic warnings. Female gender and higher CD4+ counts at the initiation of therapy place patients at greater risk of hepatic adverse events. Unless the benefit outweighs the risk, nevirapine (Viramune) should not be initiated in adult females with CD4+ cell counts greater than 250 cells/mm³ or in adult males with CD4+ cell counts greater than 400 cells/mm³. This is based on the occurrence of serious and life-threatening hepatotoxicity in controlled and uncontrolled studies. In some cases, hepatic injury has progressed despite discontinuation of treatment. It is advised that patients developing signs or symptoms of hepatitis, severe skin reaction or hypersensitivity reactions must discontinue nevirapine (Viramune) and seek medical evaluation immediately. Nevirapine (Viramune) should not be restarted following severe hepatic, skin or hypersensitivity reactions (see section on ‘Problems of Current Interest’ in the WHO Pharmaceuticals Newsletter No. 5, 2005 for a short article on hepatic adverse events with nevirapine).


Rh0(D) Immune Globulin
Intravascular haemolysis events added to label

USA. The US labelling for Rh0(D) Immune Globulin (WinRho SDF) has been updated to include safety information regarding intravascular haemolysis in patients with immune thrombocytopenic purpura (ITP) and the potential for falsely elevated blood glucose measurements in patients receiving the product. Post-marketing surveillance of Rh0(D) Immune Globulin (WinRho SDF) has revealed rare, severe and sometimes fatal, intravascular haemolysis and potentially serious complications, which include disseminated intravascular coagulation, in patients with ITP. The updated labelling advises physicians to inform patients with ITP about the symptoms of intravascular haemolysis, and to advise them to report any of these symptoms immediately. A new Patient Information Sheet will be made available to these patients. The companies also alert health-care professionals to the potential for falsely elevated blood glucose readings in non-glucose-specific testing systems, following the administration of maltose-containing Rh0(D) Immune Globulin (WinRho SDF) liquid, and advise that only glucose-specific testing systems should be used for patients receiving Rh0(D) Immune Globulin (WinRho SDF).


Telithromycin
Reports of liver toxicity

Europe. The European Medicines Agency (EMEA) has made a preliminary review of cases of serious liver injury associated with the use of telithromycin (Ketek), an antibiotic used in the treatment of respiratory infections. The reported serious liver reactions started during or immediately after treatment with telithromycin (Ketek) and were, in most cases, reversible on discontinuing treatment. Further cases of liver toxicity are being reviewed by the EMEA for a full benefit/risk assessment of the product. In the meantime, the marketing authorization holder (Aventis Pharma S.A.) has been asked to include stronger warnings of liver disorders in the telithromycin (Ketek) product information. The EMEA has issued a Press Release with this update and is reminding prescribers to use telithromycin (Ketek) with caution in patients with liver impairment (1).

USA. The FDA has issued a Public Health Advisory (2) referring to an article in the
Annals of Internal Medicine that reports three patients with serious liver toxicity following administration of telithromycin (Ketek). All three patients developed jaundice and abnormal liver function; one recovered, one required a transplant and the third died. The FDA is evaluating the issue of liver toxicity associated with telithromycin-use and, in the meantime, has provided the following recommendations to health-care providers and patients:

- Health-care providers should monitor patients taking telithromycin for signs or symptoms of liver problems. Telithromycin should be stopped in patients who develop signs or symptoms of liver problems.
- Patients who have been prescribed telithromycin and are not experiencing side effects such as jaundice should continue taking their medicine as prescribed unless otherwise directed by their health-care provider.
- Patients who notice any yellowing of their eyes or skin or other problems like blurry vision should contact their health-care provider immediately.
- As with all antibiotics, telithromycin should only be used for infections caused by a susceptible microorganism. Telithromycin is not effective in treating viral infections, so a patient with a viral infection should not receive telithromycin since they would be exposed to the risk of side effects without any benefit.

References:
**Baclofen**

Adverse reactions due to device related issues

**Canada.** Health Canada has received 21 reports of adverse reactions suspected to be associated with intrathecal baclofen (Lioresal) from 1 January 1992 to 30 June 2005, according to the latest issue of the *Canadian Adverse Reaction Newsletter*. Ten reports implicated the surgically implanted baclofen pump system; five of these reports involved problems with the catheter system and five reports involved suspected improper pump preparation leading to an inadvertent baclofen bolus dose, resulting in coma. Health-care professionals are advised to consider device-related issues when assessing the need for baclofen dose adjustments.

**Reference:**

**Clarithromycin**

Study reports fatal cardiac events

**USA.** The FDA has alerted health-care professionals to a study in Denmark that has found increased mortality from cardiac problems in heart disease patients treated with clarithromycin compared with those who received placebo. The difference in mortality in the study could be observed after ≥ one year of follow-up, but it is not clear how a two-week course of clarithromycin could increase mortality after one year. Noting that previous trials have not shown a statistically significant effect of clarithromycin on mortality, the FDA is currently not recommending changes to the use of clarithromycin (marketed as Biaxin and Biaxin XL in the United States of America). The FDA advises that further steps will be determined as more information becomes available.

**Reference:**
*FDA Alert for Health-care Professionals, December 2005 (http://www.fda.gov).*

**Colchicine**

Dosage decreased for better safety

**New Zealand.** The New Zealand Medicines and Medical Devices Safety Authority, Medsafe has advised prescribers of revised dosage advice for colchicine, as the use of high colchicine doses “is no longer appropriate” because of dose-related serious adverse effects, according to a Prescriber Update article. This advice coincides with the introduction of a colchicine 0.5 mg tablet (Colgout).

Medsafe also advises that:
- colchicine is now limited to second-line treatment for acute gout, when non-steroidal anti-inflammatory drugs (NSAIDs) are contraindicated, lack efficacy or have unacceptable adverse drug effects;
- the dosing interval has increased from two to three hourly to six hourly, the maximum daily colchicine dose is 2.5 mg in the first 24 hours and the maximum cumulative dose should not exceed 6 mg over four days;
- other treatments should be considered in elderly patients and, if using colchicine, prescribers should observe a maximum cumulative dose of 3 mg over four days;
- colchicine is contraindicated in severe renal or hepatic impairment, and concomitant renal and hepatic disease, and doses should be reduced in patients with less severe impairment or who weigh < 50 kg;
- at least three days must elapse between colchicine courses.

Medsafe also advises that patients be warned that the initial symptoms of colchicine-associated toxicity include nausea, vomiting and diarrhoea, and usually occur 2–12 hours after ingestion; if toxicity does occur, patients should discontinue colchicine immediately and seek medical advice.

**Reference:**
*Prescriber Update, December 2005, 26(2) (http://www.medsafe.govt.nz).*

**Corticosteroids (Topical)**

Reports of facial damage

**New Zealand.** The New Zealand Centre for Adverse Reactions Monitoring has received 14 reports of facial skin damage associated with the use of potent topical corticosteroids, according to a Prescriber Update article. The reports included telangiectasia, abnormal pigmentation, rosacea, perioral dermatitis, skin atrophy and striae, and were primarily associated with mometasone (Elocon), although the authors note that all topical corticosteroids used on the face carry a risk of facial skin damage, especially the more potent ones. The authors remind prescribers and patients that the use of topical corticosteroids on the face should be limited to ≤ two weeks; prescribers are advised to give clear instructions to patients about where, and how often to apply the medication.

**Reference:**
*Prescriber Update, December 2005, 26(2) (http://www.medsafe.govt.nz).*

**Gatifloxacin**

Serious effects on blood glucose levels

**Canada.** Bristol-Myers Squibb (BMS) Canada has issued a Health Canada endorsed safety information to the Canadian
products that contain glucosamine specify whether it is sourced from seafood. ADRAC warns that people who have a shellfish allergy may be more susceptible to allergic skin reactions if they ingest glucosamine obtained from seafood. Patients tolerated other glucosamine-containing product without adverse reactions in several cases reported to ADRAC.


**Immune Globulin Intravenous Reports of haemolytic reactions**

Canada. Immune Globulin Intravenous (Human), 10% (Gamunex®) belongs to a group of biological medicines derived from human plasma known as IGIV products used to treat patients with a compromised immune system or idiopathic thrombocytopenic purpura (ITP). It is administered in hospitals by infusion through the veins. Cases of haemolytic reactions associated with the use of Gamunex have been reported, according to a Health Canada-endorsed safety information from Talecris Biotherapeutics, Inc. There have been 26 reported cases of suspected haemolytic reactions associated with immune globulin (Gamunex) worldwide (20 in Canada), giving a reporting rate of 0.04% in a total of 58 949 patient-years of exposure. In the cases with information on time to onset, most reported that haemolytic reactions occurred within three days of the immune globulin (Gamunex) infusion. The reports of suspected haemolyis, haemolytic anaemia and haemolytic reactions were associated with immune globulin (Gamunex) use for either approved indications or other medical conditions; in some cases, patients received higher than recommended doses, or other risk factors for haemolytic anaemia were identified. In approximately half of the reported cases, the treatment of anaemia was not mentioned, and in the other half, treatment with blood transfusions, plasmapheresis or corticosteroids was used. Health professionals are advised to monitor patients for several days after the infusion, in case signs and symptoms of haemolysis develop (e.g. generalized weakness, lightheadedness, pale complexion and sometimes dark urine and jaundice); if symptoms occur, the health professional should confirm the diagnosis and start appropriate treatment.


**Leflunomide Reports of pneumonitis**

New Zealand. The Centre for Adverse Reactions Monitoring (CARM) has received seven reports of pneumonitis associated with the concomitant use of leflunomide and methotrexate; clinical data show that pneumonitis can also occur with leflunomide alone. The New Zealand Medicines and Medical Devices Safety Authority, Medsafe advises that early recognition of pneumonitis is important, as it can be life-threatening or cause persistent disability. Medsafe recommends that prescribers inform patients about the initial warning symptoms, so that the symptoms can be investigated immediately and the suspect drugs stopped.

Letrozole
Contraindicated in premenopausal women: a reminder

Canada. Novartis Pharmaceuticals Canada has issued reminders that letrozole (Femara) use is contraindicated in premenopausal women and that it is not authorized for the treatment of infertility (1, 2). Letrozole (Femara) is a medication authorized for use in Canada to treat breast cancer in women who are postmenopausal. Novartis advises that the company is aware that letrozole is being used for ovulation induction, and highlights warnings in the Canadian Product Monographs about the potential for maternal and fetal toxicity and fetal malformations following exposure to letrozole (Femara) (1). Novartis notes that letrozole (Femara) is also contraindicated in pregnant and lactating women and recommends that physicians administer letrozole (Femara) within the labelled indications (1); women exposed to letrozole during pregnancy should seek the advice of a physician (2).

Reference:

Oseltamivir
Interaction with warfarin

Canada. Oseltamivir (Tamiflu), an antiviral drug has been marketed in Canada since 1999. It is indicated for the treatment of acute illness due to influenza infection in patients one year and older who have been symptomatic for no more than two days. The drug is also indicated for the prevention of influenza illness in people over 13 years of age after close contact with an infected individual. From 1 January 1999, to 31 October 2005, Health Canada received 19 reports of increased international normalized ratio (INR) suspected of being associated with the use of oseltamivir. These 19 reports involved patients aged 46 to 92 years (median age 84 years), and the indication for use of oseltamivir was either treatment or prophylaxis of influenza. All of the patients were taking warfarin. The reported onset of the adverse reaction ranged from the day treatment was started to 11 days after starting oseltamivir. Six patients required treatment with vitamin K. At the time of reporting, 12 patients had recovered, two patients had not yet recovered, and the outcome was unknown for the remaining five patients. The exact mechanism is unclear at present. In addition, causality assessment of the reported cases is difficult because some of the reports presented conflicting or insufficient clinical information. In the meantime, Health Canada notes that more frequent monitoring of INRs might be prudent when oseltamivir is prescribed concurrently with warfarin and encourages health-care professionals to report any cases of INR fluctuation in patients receiving warfarin and oseltamivir concomitantly.

Reference:

Proton pump inhibitors
Reports of gynaecomastia

The Netherlands. Up until the end of June 2005, the Netherlands Pharmacovigilance Centre Lareb had received 28 reports of gynaecomastia associated with the use of proton pump inhibitors (PPIs), including omeprazole, lansoprazole, pantoprazole, esomeprazole and rabeprazole; in most reports there was a latency period of several weeks to months after start, and all reports were in men. In addition, Lareb has also received several reports of impotence, erectile dysfunction and decreased libido that may also be associated with reduced testosterone levels. According to Lareb, most of the gynaecomastia reports were associated with the use of omeprazole, and in the WHO database there was also a disproportional association with gynaecomastia and the use of other PPIs, suggesting that gynaecomastia may be a class effect of PPIs.

Reference:

Quetiapine
Urinary disorders

The Netherlands. Four reports of urinary retention and three reports of urinary incontinence associated with the use of quetiapine were received by The Netherlands Pharmacovigilance Centre, Lareb up until mid June 2005. The time to urinary incontinence onset ranged from four weeks to four months, the time to urinary retention onset ranged from three days to six months, and most patients recovered from the disorders. According to Lareb, urinary incontinence and urinary retention were disproportionately associated with the use of quetiapine in both the WHO and Lareb databases, which is indicative of a casual relationship; furthermore, both adverse reactions could be explained by
the drug's pharmacological action.


Rosiglitazone Reports of macular oedema

Canada, USA. GlaxoSmithKline (GSK) has received rare post-marketing reports of new-onset and worsening diabetic macular oedema in patients receiving rosiglitazone products (Avandia and Avandamet), used in treating type 2 diabetes mellitus. GSK advises that the visual impairment improved or resolved in some cases following discontinuation of therapy; in one case, there was resolution of the retinal oedema after a dose reduction. GSK has sent letters to health professionals in Canada (1) and in the USA (2) with the above information. The company says that the majority of patients also reported fluid retention, weight gain or peripheral oedema. In Canada health-care professionals are advised that an ophthalmological consultation should be sought, and cessation of treatment should be considered, in patients reporting visual deterioration; the company also recommends that these drugs be used with caution in patients with pre-existing retinal oedema or diabetic retinopathy. GSK advises that patients receiving rosiglitazone containing products (Avandia and Avandamet) should see their doctor if they experience blurred or distorted vision, decreased ability to adapt to darker surroundings and/or decreased colour sensitivity (3). The company recommends that patients receiving Avandia or Avandamet, who have been diagnosed with retinal oedema or diabetic retinopathy, should see their doctor to assess whether the medication should be continued. GSK emphasises that patients should not stop taking Avandia or Avandamet without first consulting their doctor (3).

References:

Shortclean Found to contain glibenclamide

Canada. The Chinese medicine, Shortclean, contains glibenclamide and phenformin that may pose a serious health risk for patients with diabetes mellitus or low blood sugar, according to a warning issued by Health Canada; Shortclean, which has been promoted for control of diabetes, is not approved for sale in Canada, and has been recently recalled by the Department of Health in Hong Kong, says the agency. Health Canada warns that people with low blood sugar or diabetes can unintentionally receive high amounts of glibenclamide by using Shortclean, and that Shortclean may increase the effects of other diabetes drugs, which may lead to a dangerous drop in blood sugar, if used concomitantly; furthermore, phenformin was removed from the Canadian market in 1977 and is banned in other countries due to reports of life threatening lactic acidosis. The agency says that patients with diabetes who use Shortclean as their only treatment, will be unable to monitor the amounts of phenformin and glibenclamide, and this could lead to potentially life-threatening, serious health risks. Health Canada advises consumers to immediately discontinue Shortclean and to seek medical attention, particularly if they are currently treated with diabetes drugs, and if they experience symptoms of low or high blood sugar. In addition, Health Canada says that Shortclean’s label is only advertised in Chinese, therefore dosage and side effect information may be unavailable to the consumer.


Statins Reports of amnesia

Canada. Health Canada has received 19 reports of amnesia suspected to be associated with statins, reported up to 31 May 2005; eight cases were associated with atorvastatin, one with cerivastatin, two with lovastatin, and four each with rosuvastatin and simvastatin. Time from treatment initiation to amnesia onset ranged from within one month to > one year; onset was not reported in four cases. Ten patients reportedly experienced positive dechallenge, and one patient reported positive rechallenge. According to Dr Michel Trottier from Health Canada, the proposed mechanism of statin-related amnesia involves statins crossing the blood-brain barrier and decreasing the amount of cholesterol required for myelin formation, resulting in demyelinated nerve fibres in the central nervous system.

Technetium (99m Tc) fanolesomab
Suspended due to safety concerns

USA. The FDA has issued a public health advisory to inform patients and health-care providers that Palatin Technologies, the manufacturer of technetium (99m Tc) fanolesomab (NeutroSpec) is voluntarily suspending marketing of this product, effective immediately, due to serious safety concerns. Technetium (99m Tc) fanolesomab (NeutroSpec) is indicated for radiologic imaging of patients with unclear signs and symptoms of appendicitis who are five years of age and older. FDA received reports from Palatin Technologies of two deaths and 15 additional life-threatening adverse events in patients receiving technetium (99m Tc) fanolesomab (NeutroSpec). These events occurred within minutes of administration of Technetium (99m Tc) fanolesomab (NeutroSpec) and included shortness of breath, low blood pressure, and cardiopulmonary arrest. Affected patients required resuscitation with intravenous fluids, blood pressure support, and oxygen. Most, but not all, of the patients who experienced these events had existing cardiac and/or pulmonary conditions that may have placed them at higher risk for these adverse events. A review of all post-marketing reports showed an additional 46 patients who experienced adverse events that were similar but less severe. The Advisory notes that there is no evidence that patients who already safely received the drug face any long-term risk.

Reference:

Warfarin Interaction with grapefruit seed extract

Sweden. A grapefruit seed extract-containing product has been suspected to interact with warfarin (Waran) therapy, according to the Swedish Medical Products Agency; the agency has received two reports. The patients had well-adjusted warfarin (Waran) dosages and had consumed the grapefruit seed extract over a period of three days; at routine check-ups, their international normalized ratios (INR values) for blood coagulation were found to have increased to 7.1 and 5.1, respectively. The agency says that grapefruit seed extract contains a substance that inhibits a warfarin-metabolizing enzyme, resulting in excessively high blood warfarin concentrations; this, in turn, increases the risks of haemorrhage and elevated INR values.

Reference:

Warfarin Serious skin reactions reported

Australia. The Australian Adverse Drug Reactions Advisory Committee (ADRAC) has received nine reports of skin necrosis associated with warfarin, three of which were fatal; the time to onset was within seven days of starting warfarin in four cases, and three to eight weeks after initiating warfarin in three cases. ADRAC advises that warfarin should be withdrawn and replaced with heparin, should skin necrosis occur. According to ADRAC, it has been suggested that starting warfarin gradually at a dosage of 1–2 mg/day to attain the desired therapeutic concentration after 10 days can reduce the necrosis risk. ADRAC says that, using this regimen, concomitant heparin can provide adequate anticoagulation initially; particular care is necessary when treating patients with risk factors such as hereditary or acquired deficiency in proteins C or S.

Reference:
Recommendations from the third meeting of the 
WHO Advisory Committee on Safety of Medicinal Products 
5-7 December 2005

The WHO Advisory Committee on Safety of Medicinal Products (ACSoMP), constituted to provide advice on pharmacovigilance policy, and issues related to the safety and effectiveness of medicinal products, held its third meeting in December 2005. The following is a summary of the minutes of the meeting.

The WHO Collaborating Centre for International Drug Monitoring (Uppsala Monitoring Centre, the UMC)

Two current important issues of the UMC are: (1) sustainability and (2) the funding of resources. Ninety per cent of the budget of the UMC is income from sales of UMC commercial products. The UMC runs the programme for least developed nations with the resources generated by marketing UMC products to well-developed, research-based industries. Concern was raised that the UMC is becoming too commercial in its operations and it was strongly suggested that a better budget allocation be obtained at the highest level of WHO.

Pharmacovigilance for antiretrovirals (ARVs)

ACSoMP has been asked to propose recommendations for safety systems within the HIV/AIDS programme and design specific studies with an action plan. This is a follow up of discussions on the need for pharmacovigilance in public health programmes, at the Twenty-eighth Annual Meeting of Representatives of the National Centres participating in the WHO Programme for International Drug Monitoring. Encouragement is sought on how to collect adverse drug reaction (ADR) reports. Some sites are looking at toxicities and the consequences of combinations. Issues around guidelines for use of ARVs in paediatrics, use of drugs in pregnancy (registers) and in patients with co-morbidities were also raised.

Action points:
- A small working group will deliver a pharmacovigilance action plan for a pilot project in a few sites in Africa, to work with the WHO HIV/AIDS programme and strengthen spontaneous ADR reporting, monitoring of specific toxicities and using a pregnancy register. The proposal will also include a suggested budget and will be prepared by the end of January 2006, at which stage the HIV/AIDS programme will be consulted for their input.
- The HIV/AIDS programme will be asked to help identify individuals within the target countries in executing the approved version of the action plan. In writing the proposal, the working group would need access to the following information: pregnancy monitoring programme, other drugs being used in the HIV/AIDS programme.
- The methodology for monitoring pregnancy should be as in other WHO programmes, to avoid confusion in the field.
- The HIV/AIDS programme should be supplied with the new publication in the Safety Monitoring of Medicines series, ‘The safety of medicines in public health programmes: pharmacovigilance an essential tool’.

Patient Safety initiatives

1) Patient safety pilot project
ACSoMP members were presented with a four-year pilot project to incorporate the collection of medication errors into pharmacovigilance programmes. ACSoMP strongly supported this initiative but expressed concern that this was an ambitious project that would require additional resources.

Action points:
ACSoMP requested that the following principles be applied in furthering the project:
- Activities should serve to strengthen the principle objective of the national pharmacovigilance centres, which is the promotion of the science-based practice of pharmacovigilance.
- It should strengthen the capacity and self-sufficiency of the National Centres (financial sustainability in the short and long term).
- The principal focus should be on developing countries.
- There must be a clear cut leadership from the WHO Quality Assurance and Safety of Medicines (QSM) team and the UMC on this programme.
- There must be a clear system for intelligence sharing and the translation of lessons learnt into policy.
2) WHO draft guidelines for adverse event reporting and learning systems
ACSoMP noted the draft manuscript recently published by the Patient Safety department in WHO. This had been issued without the normal consultative process within WHO. ACSoMP members expressed their disappointment that no mention was made of the work done by WHO/QSM and the UMC in the areas of pharmacovigilance and drug safety. They suggested that the department of Patient Safety should seriously consider including a section on the work of WHO/QSM and the UMC into this draft. Furthermore, they requested that their comments would be taken into account in revising this manuscript.

Action point:
• A section describing the work of the UMC should be drafted for immediate insertion into the draft document. ACSoMP members will provide extensive comments on the manuscript by end of January.

3) Advocacy
A draft of a pharmacovigilance advocacy paper was discussed. The paper outlines the strategic directions for medicine safety and the WHO Programme for International Drug Monitoring in the next few decades. It suggests developing a strategy for the promotion of medicine safety around the world through a network of dedicated advocates, such as the WHO partners and National Centres.

Action points:
• To initiate discussions on pharmacovigilance at the political level and at WHO higher offices; to submit a proposal to the World Alliance for Patient Safety to integrate pharmacovigilance into the Alliance; to suggest yearly pharmacovigilance themes targeted at specific population groups; to introduce the concept of a worldwide Pharmacovigilance Day.
• WHO may need to have some high level endorsements from ministries of health so that pharmacovigilance centres can move forward in promoting safety of medicines and find ways to integrate pharmacovigilance into the health policy of the country.
• A paper will be prepared and submitted to the World Alliance for Patient Safety.

WHO International Classification and Taxonomy
The International Classification of Diseases (ICD) team, from the WHO Family of International Classifications presented their work to ACSoMP members and showed how it related to pharmacovigilance. The ICD-11 is under preparation and the department needs the input of experts in the area of safety monitoring to review its section on Drugs, medicaments and biological substances causing adverse effects in therapeutic use. The team highlighted the need to harmonize terminologies throughout WHO.

Action point:
• WHO/QSM and the UMC will collaborate with the WHO Family of International Classifications.

Safety of medicines in children
ACSoMP has recommended that WHO address the issue of safety of medicines in children and that a guideline be prepared. The actions taken so far include approaching Karolinska Institute for preparing the first draft manuscript on the safety of medicines in children. This project is currently in the development phase. A document prepared by one of the ACSoMP members was presented. ACSoMP decided that the document needs to be strengthened with additional input.

Action point:
• Members to convey any comments on the presented document by the end of the year. The revised document will be an internal document to guide National Centres and can be posted in the new UMC website under the section on Practical Pharmacovigilance.

Report on kava
In the previous meeting, ACSoMP had commissioned an investigation on reports of hepatotoxicity with kava. The resulting report contains extensive analysis of various available literature (case reports, clinical trials, etc). The conclusions and recommendations were presented to ACSoMP.

Action points:
• ACSoMP to endorse this research and use the inquiry team’s recommendations in drafting a WHO position paper. Drug regulatory authorities should be consulted for their views on the recommendations, for additional input to the WHO position paper. More time is needed for ACSoMP members to review specific documents used in the investigation; comments from members of ACSoMP should be sent to the authors by the end of January 2006; a revised document will be produced by the end of March, to be followed by six weeks of consultations and a final teleconference in mid-June 2006.
**Safety of specific products**

**Amodiaquine/artesunate**
Ghana has switched to using amodiaquine and artesunate combinations in the treatment of malaria in the light of resistance to chloroquine and sulfadoxine/pyrimethamine. Reports of ADRs to this combination are emerging from Ghana and also verbal reports from Nigeria and Sierra Leone. These reports include dystonic reactions. A letter to The Lancet was drafted describing the situation. ACSoMP wished to have more information on the reports.

**Action point:**
- The reports should be investigated further. Risk minimization plans should be put in place so that situations such as the present crisis do not have a negative impact on the malaria programme.

**Levamisole**
This medicine was discussed at the Twenty-eighth Annual Meeting of National Centres participating in the WHO Programme for International Drug Monitoring. Concerns were raised by China that leukoencephalopathy followed the use of levamisole. This had resulted in the removal of this medicine from the national formulary by the Chinese government. This drug is in the WHO Model Formulary; but since many countries have withdrawn levamisole, the overwhelming data on toxicity should be communicated to the Essential Medicines Programme. However, it was noted that the WHO Expert Committee on Essential Medicines will not meet until 2007.

**Action point:**
- A member country (i.e. China) will communicate to the WHO Essential Medicines Programme about this new finding and apply for a formal de-listing of the drug from the Essential Medicines List (EML). The information regarding levamisole-induced leukoencephalopathy will be sent out to WHO Member States as a WHO Information Note. For those years when the Expert Committee do not meet, the WHO Essential Medicines Programme should introduce a process of interim consultation for the rapid suspension and de-listing of medicines from the EML.

**Moxifloxacin**
There has been some discussion on E-drug (electronic discussion group) about introducing moxifloxacin as a suggested treatment for resistant tuberculosis (TB) in the directly observed treatment short-course-plus (DOTS-plus) programme since the drug could potentially lower the treatment duration to four months. There is lack of data on the long-term safety with moxifloxacin. There are 4200 case reports in the WHO (UMC) database from 30 countries. These ADR reports are probably from short-term use. There are concerns that the drug is expensive, and that the drug on long-term use can lead to resistance of other bacteria. However, ADR data from short-term use should not be extrapolated to reflect effects from long-term use. Additionally, there is a need to make a statement about contraindications for use in pregnancy and in children.

**Action point:**
- Information must be sought from available clinical trials on the efficacy and safety from long-term use of moxifloxacin before any risk/benefit recommendations can be made.

**Oseltamivir**
The WHO background work on the efficacy and safety of antiviral drugs during influenza pandemics was presented. As a consequence of the work started in 2002 and carried out by 30 experts, a WHO guideline was produced. However, data for 2004 is not included in the guideline. In August 2005, the pharmaceutical company Roche donated three million treatment courses of the medicine oseltamivir towards a WHO international antiviral stockpile. It is necessary that the efficacy and safety of this medicine is adequately documented, both prior to, and during the possible flu pandemic.

**Action points:**
- Roche should be asked by WHO to assist with the development of a system of active surveillance for countries using oseltamivir in mass treatment during influenza pandemics. Particular attention should be given to pregnant women taking this drug.
- Reports and documents should be reviewed with the addition of a section on intensive monitoring of at least 10 000 patients as part of the pharmacovigilance assessment.
- Issues of counterfeit products should also be considered. The company should be asked to take part in the intensive monitoring programme, as part of the product stewardship.
Tenofovir and emtricitabine
Information was presented that a new combination of these two drugs is being reviewed. Concerns include the need to have renal effects in the safety profile. This drug is being promoted as first-line treatment in the HIV/AIDS programme; hence, this safety concern.

Action point:
- The Advisory Committee will be kept informed of further developments.