WHO PHARMACEUTICALS NEWSLETTER

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

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

Further information on adverse reactions may be obtained from the WHO Collaborating Centre for International Drug Monitoring, Stora Torget 3, 753 20 Uppsala, Sweden. Tel: 46-18-65.60.60 Fax: 46-18-65.60.80 E-mail: sten.olsson@who-umc.org Internet: http://www.who-umc.org

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News & Issues

More definite regulatory actions have now been taken in some countries, either for specific cyclooxygenase-inhibitors or for the non-steroidal anti-inflammatory drugs as a whole; the most recent decisions are included in this issue. A list of recently prequalified drugs is also included as part of our promise to familiarize readers with the work of the WHO prequalification team.

Preparations are under way for the Twenty-eighth Annual Meeting of Representatives of National Centres participating in the WHO International Drug Monitoring Programme, to be held in Geneva, 26 - 29 September 2005. In addition to various other collaborative features, this year's meeting will include a working group exercise on patient safety, to determine how national pharmacovigilance centres could work with the World Alliance for Patient Safety. The draft agenda for the meeting is published with this edition for your information. We hope to see many of you at the meeting.
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'Antiretroviral agents: Caution advised against certain combinations. Canada. Bristol-Myers Squibb and Gilead Sciences have issued a 'Dear Health-care Professional' letter to highlight that new clinical data show the potential for drug interactions between didanosine (delayed-release capsules enteric coated beadlets, Videx EC) and tenofovir disoproxil fumarate (Viread), with or without efavirenz (Sustiva) or nevirapine (Viramune). According to reports from recent investigator-sponsored studies, the coadministration of tenofovir and didanosine with either efavirenz or nevirapine may be associated with a potentially high virological failure rate and emergence of resistance in antiretroviral-naive adults with HIV-infection, low CD4+ cell counts and high baseline viral loads. Results of pharmacokinetic studies show that tenofovir and didanosine coadministration increases systemic didanosine exposure by 40–60%, and could potentiate didanosine-related adverse events (AEs). The companies recommend that the coadministration of didanosine and tenofovir be undertaken with caution, that patients who are receiving both drugs be monitored carefully for continued efficacy and for AEs, and that didanosine be discontinued in patients who develop AEs associated with the drug. The companies advise that the Canadian didanosine (Videx EC) and tenofovir disoproxil fumarate (Viread) product monographs have been revised to include this information, along with recommended didanosine dosage adjustments for coadministration with tenofovir.

Reference:
Atypical Antipsychotics: Risk of death in elderly patients with dementia. Canada, USA. Health Canada is advising consumers about the increased risk of death in elderly patients with dementia receiving atypical anti-psychotics (1). The Advisory applies to clozapine (Clozaril), risperidone (Risperdal), quetiapine (Seroquel) and olanzapine (Zyprexa) and is based on recent trials that found that elderly patients with dementia receiving atypical anti-psychotics had a 1.6-fold greater death rate than those receiving placebo. Health Canada is requesting that all manufacturers of these drugs add a warning highlighting this risk to their safety information sheets. The agency is advising patients to continue taking their medication as usual and to contact their doctor with any concerns. The US FDA has issued a Public Health Advisory highlighting the increased death rate associated with the use of atypical antipsychotics for behavioural disorders in elderly patients with dementia, and has also requested that manufacturers add a boxed warning (2). (See WHO Pharmaceuticals Newsletter No. 2, 2004 for similar warnings issued by the European Medicines Agency (EMEA) and the UK Committee on Safety of Medicines concerning the use of olanzapine and risperidone in the elderly population).

References:

**Cyclooxygenase-2 (COX-2) Inhibitors To be available under strict restrictions**

New Zealand. Following the recommendations made by New Zealand's Medicines Adverse Reactions Committee (MARC), the country's Ministry of Health has decided that COX-2 inhibitors will be allowed to stay on the market, but with "considerably stronger warnings"(1). New Zealand's Medicines and Medical Devices Safety Authority (Medsafe) has sent a fax to doctors and pharmacists communicating this decision, along with the following recommendations (2):

- COX-2 inhibitors should be contraindicated in patients with previous myocardial infarction (MI) or stroke and perioperatively for cardiac or vascular surgery, and perioperatively for major surgery in patients at high cardiovascular (CV) risk.
- Etoricoxib should be contraindicated in patients with poorly controlled hypertension.
- COX-2 inhibitors should not be used if alternatives exist, and, if used, the lowest effective dose should be used for the shortest possible duration.
- Patients should be reviewed after 2 weeks, with treatment discontinued in the absence of benefit, then reviewed every 3 months.
- Prescribers need to be aware that COX-2 inhibitors may exacerbate hypertension, cardiac failure or oedema.
- Prophylactic aspirin should not be discontinued.

- All patients at high CV risk should be informed of the risks with COX-2 inhibitors.
- Discussions regarding perioperative use of COX-2 inhibitors should be undertaken prior to surgery. Medsafe is in the process of implementing MARC's recommendations and has asked that pharmaceutical companies continue with the voluntary moratorium on direct-to-consumer and professional advertising of COX-2 inhibitors.

**References:**

**Cyproterone acetate and ethinylestradiol Not to be used in contraception**

Canada. Health Canada is advising consumers that the authority has reached an agreement with Berlex, manufacturer of ethinylestradiol/cyproterone (Diane-35) on revised labelling for its use in Canada. The following warnings are included on the new package insert:

- Ethinylestradiol/cyproterone (Diane-35) must not be used in women who currently have, or have a history of, thromboembolic disorders or thrombophlebitis.
- Ethinylestradiol/cyproterone (Diane-35) should not be prescribed for contraception alone.
- Women should not use oral contraceptives during ethinylestradiol/cyproterone (Diane-35)-treatment.
- Ethinylestradiol/cyproterone (Diane-35) should be stopped 3–4 months after the complete resolution of the signs of acne.

Patients are advised to inform their doctor if they currently have, or have a history of, blood clots, myocardial infarction, stroke or chest pain.

**References:**

**Donepezil Warning of rhabdomyolysis**

Japan. The Ministry of Health, Labour and Welfare in Japan has added a new warning on the possibility of rhabdomyolysis associated with the use of donepezil (Aricept), an acetylcholinesterase inhibitor drug. The Ministry enforced this action following the death of a 70 year-old man with Alzheimer's disease and other complications who was treated with this drug. The warning advises that treatment should be halted if muscle pain, elevated urine/blood myoglobin levels or acute kidney failure are detected.

**Reference:**
### Drotrecogin alfa (activated)
**Only for use in high-risk patients**

**Europe.** The EMEA’s Committee for Medicinal Products for Human Use (CHMP) has recommended drotrecogin alfa (Xigris) be used only in high-risk patients (that is patients at a high risk of death from sepsis associated with acute organ dysfunction) and when therapy can be started within 24 hours of organ failure. Additionally, the committee has recommended that drotrecogin alfa (Xigris) be used only by experienced doctors in institutions skilled in the care of patients with severe sepsis, and that the agent should not be used in patients with single organ dysfunction, especially if they have had recent surgery. It may be recalled that some months ago Eli Lilly had issued letters to health professionals in Canada and in the US warning about a higher mortality in patients treated with drotrecogin alfa compared to placebo (see WHO Pharmaceuticals newsletter No. , 2005).

**Reference:**

### Efavirenz
**Reports of neural tube defects**

**USA.** Bristol-Myers Squibb has issued a ‘Dear Health-care Provider’ letter advising of a change in the pregnancy category for efavirenz (Sustiva) from Category C (risk of fetal harm cannot be ruled out) to D (positive evidence of fetal risk), following four retrospective reports of neural tube defects (three cases of spina bifida cystica and one of Dandy Walker syndrome) in infants born to women who received efavirenz in their first trimester of pregnancy. Bristol-Myers Squibb warns that, prior to initiation of efavirenz (Sustiva), women of childbearing potential should undergo pregnancy testing. The company also recommends that women receiving efavirenz (Sustiva) should avoid pregnancy, and that efavirenz (Sustiva) should be used during the first trimester only "if the potential benefit justifies the potential risk to the fetus".

**Reference:**

### Efalizumab
**Immune mediated haemolytic anaemia**

**USA.** Genentech has issued a new warning regarding events of immune-mediated haemolytic anaemia associated with efalizumab-use, indicated in the treatment of severe plaque psoriasis in adult patients (18 years or older). According to Genentech, two cases of haemolytic anaemia were observed in efalizumab (Raptiva) clinical trials; two additional cases were reported in the postmarketing setting. In its letter to health-care providers Genentech has stated that a causal relationship between efalizumab (Raptiva) and these events has not been established but cannot be excluded and that health-care providers should discontinue treatment if haemolytic anaemia occurs.

**Reference:**

### Galantamine
**Death in subjects with mild cognitive impairment**

**USA.** The prescribing information for galantamine (Reminyl) has been updated to reflect the results of two randomised placebo-controlled clinical trials in which 13 of 1026 patients with mild cognitive impairment receiving galantamine (Reminyl) died, compared with 1 of 1022 patients who received placebo. Ortho-McNeil Neurologics Inc. has issued a ‘Dear Health-care Professional’ letter to advise that the results of these trials have been added to the Precautions section of the Reminyl Prescribing Information. In this letter, Ortho-McNeil Neurologics Inc. notes that galantamine (Reminyl) is approved only for the treatment of mild to moderate Alzheimer’s disease.

**Reference:**

### Hydromorphone hydrochloride
**To be withdrawn for safety reasons**

**USA.** The FDA has advised Purdue Pharma to suspend the sales and marketing of hydromorphone hydrochloride (Palladone) controlled-release capsules in the US, as co-ingestion of the drug with alcohol may cause severe adverse effects, such as depressed breathing, coma and even death. The FDA is not aware of any reports of life-threatening adverse effects in patients drinking alcohol while receiving hydromorphone, which has been for sale in the US since January 2005. However, the results of a recent company-sponsored
pharmacokinetic (PK) study show that the co-ingestion of alcohol affects hydromorphone hydrochloride's controlled-release mechanism, which may lead to the rapid release of hydromorphone and result in high peak plasma hydromorphone concentrations; during the co-ingestion of hydromorphone and 4% alcohol, some subjects developed almost twice the peak plasma hydromorphone concentration observed with the ingestion of hydromorphone hydrochloride and water. Based on available data, the agency has concluded that the overall hydromorphone hydrochloride (Palladone) risk/benefit profile is unfavourable because of this potentially fatal interaction.

The FDA advises health-care providers, who have prescribed hydromorphone hydrochloride, to contact patients who are affected, to advise them not to use hydromorphone with concomitant alcohol, and to prescribe an appropriate substitute. Patients receiving hydromorphone hydrochloride (Palladone) are advised to contact their physician to discuss alternative treatment, including immediate-release hydromorphone, and to avoid alcohol, or medicines containing alcohol, on the days that they take hydromorphone. The FDA recommends that unused hydromorphone hydrochloride (Palladone)-capsules should be flushed down the toilet for safe disposal.

Reference:

Lepirudin
Information on dosage and administration

Canada. Berlex Canada Inc., in consultation with Health Canada, has revised the Product Monograph for lepirudin (REFLUDAN), indicated for anticoagulation in patients with heprrin induced thrombocytopenia (HIT) and associated thromboembolic disease in order to prevent further thromboembolic complications. As of April 25, 2005, the product monograph has been updated with the following information:

- Serious thrombotic events can occur in HIT patients. Caution should be exercised in the timing of drug administration during the transition period between discontinuing parenteral anticoagulation therapy, such as lepirudin (REFLUDAN), and starting oral anticoagulation.
- Coumarin derivatives should only be initiated when platelet counts are normalizing. The intended maintenance dose should be started with no loading dose. To avoid prothrombotic effects when initiating coumarin, lepirudin (REFLUDAN) should be continued for 4 to 5 days and discontinued when the International Normalized Ratio (INR) stabilizes within the desired target range.

In a letter to health professionals, Berlex Canada Inc. writes that 'coumarin therapy be avoided during acute HIT and only be initiated after a substantial recovery of the platelet count has occurred. This is based on current scientific knowledge of coumarin-induced hypercoagulability during initiation of vitamin K antagonists, as presented in the literature. There is one published case report of venous limb gangrene involving a lepirudin-treated patient in the US'.

Reference:

Mitoxantrone
Label to reflect risks of cardiotoxicity

USA. Mitoxantrone (Novantrone) is approved for use in patients with secondary progressive, progressive relapsing, or worsening relapsing-remitting multiple sclerosis. In the US, mitoxantrone (Novantrone) label has been revised to state that cardiac monitoring should be performed at baseline, and before every dose of mitoxantrone, in patients with multiple sclerosis receiving the drug. The revisions follow post-marketing reports that show diminished cardiac function in patients occurring early on in treatment with the product. The Boxed Warning, Warnings, and Dosage and Administration sections of the label have been revised.

Reference:

NSAIDs
Black box warning for both prescription and OTC products

USA. FDA has requested that sponsors of all non-steroidal anti-inflammatory drugs (NSAID) make labelling changes to their products. The FDA has recommended label changes for both the prescription and over-the-counter (OTC) NSAIDs and a medication guide for the entire class of prescription products. All sponsors of marketed prescription NSAIDs, including Celebrex (celecoxib), a cyclooxygenase-2 (COX-2) selective NSAID, have been asked to revise the labelling (package insert) for their products to include a boxed warning, highlighting the potential for increased risk of cardiovascular (CV) events and the well described, serious, potentially life-threatening
gastrointestinal (GI) bleeding associated with their use. The agency based its advice on a review of the regulatory histories and databases on the various NSAIDs.

Reference:

Oxcarbazepine
Label to include serious dermatological reactions

Canada, USA. Novartis Pharmaceuticals has issued a 'Dear Health-care Provider' letter to advise of additions to the Warnings and Precautions sections of the US labelling for oxcarbazepine (Trileptal), indicated in the treatment of partial seizures in adults and children with epilepsy. The letter advises that the Warnings section of the oxcarbazepine (Trileptal) label has been updated to include information regarding an increased risk of Stevens-Johnson syndrome and Toxic Epidermal Necrolysis in patients receiving the agent. According to Novartis, post-marketing reporting rate for these events currently exceeds the background incidence rates by a factor of 3-10 fold, with most cases occurring within the first month. Additionally, the Precautions section now includes information on multi-organ hypersensitivity reactions occurring in close temporal association to the initiation of oxcarbazepine (Trileptal)-treatment, with some reports of cases resulting in hospitalization.

Reference:
2. 'Dear Health-care Provider' letter from Novartis Pharmaceuticals Corporation, USA, 27 April 2005 (http://www.fda.gov).

Paroxetine and Pimozide
Concurrent use contraindicated

Canada. GlaxoSmithKline Inc. (GSK), following discussions with Health Canada, is advising physicians against the concurrent use of paroxetine (Paxil and Paxil CR) and pimozide, since paroxetine was found to increase plasma pimozide levels in an open-label study of healthy volunteers who were administered both drugs. Elevation of pimozide blood concentration may result in QT interval prolongation and severe arrhythmias including Torsade de Pointes.

Reference:

Phenylpropanolamine
Suspended while adverse reaction reports are reviewed

Portugal. The Portuguese regulatory body, Infarmed, has suspended cold and flu products containing the decongestant phenylpropanolamine (PPA), while it reviews PPA’s risk/benefit profile following worldwide concerns of cerebral haemorrhage and other adverse reactions. It may be recalled that PPA-containing products were withdrawn in several countries following the publication of an article (N Eng J of Med, 2000; 343: 1826-32) that reported a risk of haemorrhagic stroke associated with the use of PPA. (Also see WHO Pharmaceuticals Newsletters No. 4, 1996 and No. 5, 2004).

Reference:
Boletim de Farmaco Vigilancia, 2005, 9(2).

Sildenafil, Tadalafil, Vardenafil
Labels updated with NAION information

USA. The FDA has notified health-care professionals of updated labelling for tadalafil (Cialis), vardenafil (Levitra) and sildenafil (Viagra) to reflect a small number of postmarketing reports of sudden vision loss, attributed to a NAION (non arteritic ischaemic optic neuropathy), a condition where blood flow is blocked to the optic nerve. All three preparations are indicated in the treatment of erectile dysfunction in men. The FDA advises patients to stop taking these medicines, and call a doctor or health-care provider right away if they experience sudden or decreased vision loss in one or both eyes. Patients taking or considering taking these products should inform their health-care professionals if they have ever had severe loss of vision, which might reflect a prior episode of NAION. Such patients are at an increased risk of developing NAION again. At this time, it is not possible to determine whether these oral medicines for erectile dysfunction were the cause of the loss of eyesight or whether the problem is related to other factors such as high blood pressure or diabetes, or to a combination of these problems.

Reference:
Valdecoxib
Sales suspended in more countries

Canada, Europe, India. Pfizer has voluntarily suspended the sale of valdecoxib (Bextra) in the EU countries (1) and in Canada (2), at the request of the respective regulatory agencies. It may be recalled that Pfizer agreed to similar actions in the United States (WHO Pharmaceuticals Newsletter No. 2, 2005). The suspension is effective pending further safety reviews. Health Canada has stated that satisfactory safety evidence needs to be established with respect to the review of cardiovascular, gastro-intestinal and rare but potentially life-threatening skin reactions such as Stevens-Johnson Syndrome, toxic epidermal necrolysis and erythema multiforme. Agencies are advising prescribers not to initiate treatment of new patients, to monitor carefully patients being treated with valdecoxib (1) or to switch to alternative therapy, where appropriate (2). Ranbaxy Laboratories in India has voluntarily discontinued sales of its valdecoxib formulations (3). Ranbaxy’s decision comes even as valdecoxib is being reviewed by India’s Drug Controller General for its benefit/risk profile. Selective COX-2 inhibitors such as celecoxib, parecoxib, valdecoxib and etoricoxib are required to carry a ‘precautionary warning’ on their labels and promotional literature in India (see WHO Pharmaceuticals Newsletter No. 2, 2005).

References:

Veralipride
Suspended due to neurological and other adverse reactions

Spain. Effective June 2005, the Spanish Agency for Medicines and Medical Devices has suspended the marketing authorization for veralipride (Agreal) in Spain. This action is based on the conclusions of the Spanish Medicines Safety Committee that reviewed reports of psychiatric and neurological disorders and of withdrawal symptoms associated with veralipride use. The Agency has released a press statement on its website and has communicated this information to all health professionals in the country.

Reference:
Angiotensin converting enzyme (ACE)-Inhibitors
Continuing reports of angioedema

Australia. The Australian Adverse Drug Reactions Advisory Committee (ADRA) has received > 7000 reports of angioedema since 1970, 916 (12.6%) of which were associated with ACE-inhibitors. Although ADRA first advised of the potentially life-threatening angioedema risk associated with ACE-inhibitors in 1993, the Committee has continued to receive reports, including two recent cases: one involved an elderly woman who developed angioedema after receiving ramipril for a year, and the other involved a patient who experienced 20 episodes of angioedema over 12 months before an association with his perindopril therapy was made. ADRA has also received 119 reports of angioedema with angiotensin II-receptor antagonists, and warns that patients who have a history of ACE-inhibitor-associated angioedema may also develop angioedema with angiotensin II-receptor antagonists.

Reference:
Adverse Drug Reactions Advisory Committee.

Anticonvulsants
Drug-suicide link to be reviewed

USA. The US Food and Drug Administration (FDA) has asked Pfizer and 13 other manufacturers of anti-epilepsy drugs to re-examine their clinical trial data for evidence of increased drug-induced suicide and/or suicidality. The 14 companies have been asked to re-analyse their clinical trials data in six months after which the FDA will conduct final analyses. The FDA has advised the re-analysis following some signals that were observed in controlled trial databases for currently marketed anticonvulsants and due to postmarketing concerns of suicides by patients taking gabapentin (Neurontin), an anti-epilepsy preparation that is marketed in the US.

Reference:

Ayurvedic Medicines
Some contain high levels of heavy metals

Canada. Health Canada has issued a warning to consumers not to use certain Ayurvedic medicinal products as they contain high levels of heavy metals that may pose a health risk. The agency has so far found a number of unapproved Ayurvedic products available on the Canadian market that contain high levels of lead, mercury and/or arsenic, and says that action is being taken to remove these products from the market and to stop their importation into Canada. Health Canada is advising consumers who have used these products, and are concerned about their health, to seek advice from a health professional; consumers with these products should contact their Municipal Government regarding the safe disposal. Health Canada recommends that Canadians only use Ayurvedic products that have been authorised for sale by the agency. (Health Canada had also issued a related advisory in March 2005; see WHO Pharmaceuticals Newsletter No. 2, 2005).

Reference:

Antidepressants
Monitoring adults for suicidality

USA. The US FDA has issued a Public Health Advisory to highlight that adults receiving antidepressants should be closely monitored for signs of worsening depression or increased suicidality, in response to several recent scientific publications that have suggested a possible increased risk of suicidality in such patients. The FDA has advised that a complete review of all available data has started, in order to establish whether the risk of suicidality is increased in adults receiving antidepressants, but that the review will most likely take at least a year to complete. Although the FDA's current recommendations (close monitoring and evaluation by a health-care professional if increased suicidality occurs) are consistent with existing label warnings, the information will also be added to the Patient Information and Health-care Professional Sheets for the antidepressant indications.

References:

Antidepressants
Use in children

Europe. The European Medicines Agency (EMEA) has completed its review of serotonin-selective reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs) and has concluded that these...
agents should not be used in children and adolescents except for their approved indications. The EMEA’s Committee for Medicinal Products for Human Use (CHMP) examined the potential risk of suicidal behaviour in children and adolescents receiving these antidepressants, and concluded that suicide-related behaviour and hostility were observed more frequently in children and adolescents receiving antidepressants than in those receiving placebo. The CHMP is recommending issuing strong warnings across the EU to both doctors and patients about these risks, and doctors and patients will be advised that these products should not be used for the treatment of children and adolescents except for their approved indications, which for some of these antidepressants include obsessive-compulsive disorder and attention-deficit hyperactivity disorder.


Dextromethorphan Abuse may be deadly

USA. 'Dextromethorphan abuse is potentially harmful and may result in death, the US FDA has warned in a recent Talk Paper. The FDA advises of five recent reports of teenage deaths that may have been associated with the consumption of encapsulated pure dextromethorphan in powdered form. The FDA warns that, although dextromethorphan is generally safe at recommended doses, abuse can lead to death or serious adverse events such as seizure, loss of consciousness, brain damage and arrhythmias. Although dextromethorphan abuse is not new, the FDA says that the sale of the pure powdered form is a disturbing new trend.


Fentanyl transdermal patches Safety warnings regarding use

USA. The FDA has issued a Public Health Advisory to alert patients and health-care providers to the dangers associated with fentanyl (Duragesic as well as generic preparations of fentanyl), and to provide recommendations on the safe use of the drug. The FDA reports that serious adverse effects, overdoses and death have occurred in patients using transdermal fentanyl patches for pain control, and that these cases are being investigated. The FDA highlights the following:

- Fentanyl patches are very strong opioid analgesics, and an overdose may be fatal. The patches should always be prescribed at the lowest dose needed.
- Fentanyl patches should not be used to treat short-term, postoperative or inconstant pain, and should only be used by opioid-tolerant patients who have chronic pain that is not well-controlled with shorter-acting analgesics.
- Patients using fentanyl patches and their caregivers should be advised to follow the directions for safe fentanyl use exactly.
- Patients using fentanyl patches and their caregivers should be advised that the patches should be stored in a safe place, out of children’s reach, and that any used, defective or un-needed patches should be discarded safely by folding the sticky side of the patch together and flushing it down the toilet.
- Patients using fentanyl patches, their caregivers and prescribers should be aware of the signs of fentanyl overdose; if these occur, patients or their caregivers should seek medical attention immediately.
- Patients using fentanyl patches may experience a stronger effect or a sudden and potentially dangerous increase in fentanyl concentration if they are exposed to heat, have an increase in body temperature, use concomitant alcohol, or use drugs that affect fentanyl metabolism or affect brain function.


Fluorescein Recommendations for safe use

France. The French Agency for the Medical Safety of Health Products, AFSSAPS, has noted an increase in the number of reports of severe adverse events in association with fluorescein (AK-Fluor), in particular, allergic reactions. By October 2004, the agency had received 23 such cases, five of which had a fatal outcome. As a precaution, AFSSAPS recommends that prescribers avoid fluorescein angiography in conditions/diseases where there is no benefit from the procedure. AFSSAPS reminds prescribers to take a detailed history and to monitor patients closely during, and for 30 minutes after, the procedure. A letter has been sent to relevant health-care professionals regarding this information.

Interferon alfa-2b
Reports of osteonecrosis

Australia. Australia's Adverse Drug Reactions Advisory Committee (ADRAC) has received a total of 426 reports involving interferon-α-2b and, of these, six reports were of avascular necrosis, osteonecrosis or aseptic necrosis, associated with treatment of chronic myeloid leukaemia (CML). Bone or MRI scans identified necrosis on femoral or humoral heads in these patients who had received daily doses of interferon-α-2b of 3–10 million units; time to onset was 3–8 weeks.


Isotretinoin
Update on reports of suicidal thoughts

Australia. The Australian Adverse Drug Reactions Advisory Committee (ADRAC) has received 21 reports of suicidal ideation or attempts associated with isotretinoin (Accure, Oratane, Roaccutane)-use. The reports involved patients aged 13–40 (median 18) years, and fatal outcomes were documented in two cases. ADRAC agrees that severe acne can affect a patient's self-esteem, leading to depression. However, ADRAC advises that patients and their families should be made aware of the risk of depression when isotretinoin is prescribed, and the importance of seeking urgent reassessment if signs of depression develop.


Mifepristone and misoprostol
Reports of septic deaths

USA. The FDA has received four reports of septic deaths in women in the United States, from September 2003 to June 2005, following medical abortion with mifepristone (Mifeprex) and misoprostol. The bacteria causing sepsis has been identified in two of the cases as Clostridium sordellii. The other two cases are under ongoing investigation by FDA along with the Centers for Disease Control and Prevention, State and local health departments, and the manufacturer of mifepristone (Mifeprex). All cases involve the off-label dosing regimen consisting of 200 mg of oral mifepristone (Mifeprex) followed by 800 mcg of intravaginally placed misoprostol. The FDA has issued a Public Health Advisory with the following recommendations:

- All providers of medical abortion and emergency room health-care providers should investigate the possibility of sepsis in patients who are undergoing medical abortion and present with nausea, vomiting, or diarrhea and weakness with or without abdominal pain, and without fever or other signs of infection more than 24 hours after taking misoprostol. To help identify those patients with hidden infection, strong consideration should be given to obtaining a complete blood count.

- FDA recommends that physicians suspect infection in patients with this presentation and consider immediately initiating treatment with antibiotics that includes coverage of anaerobic bacteria such as Clostridium sordellii.

- At this time FDA does not have sufficient information to recommend the use of prophylactic antibiotics. Reports of fatal sepsis in women undergoing medical abortion is very rare (approximately 1 in 100,000). Prophylactic antibiotic use carries its own risk of serious adverse events such as severe or fatal allergic reactions. Also, prophylactic use of antibiotics can stimulate the growth of “superbugs,” bacteria resistant to everyday antibiotics. Finally, it is not known which antibiotic and regimen (what dose and for how long) will be effective in cases such as the ones that have occurred.

- The approved mifepristone (Mifeprex) regimen for a medical abortion through 49 days’ pregnancy is:
  - Day One: mifepristone (Mifeprex) Administration: 3 tablets of 200 mg of mifepristone (Mifeprex) orally at once.
  - Day Three: Misoprostol Administration: 2 tablets of 200 mcg of misoprostol orally at once.
  - Day 14: Post-Treatment: the patient must return to confirm that a complete termination has occurred. If not, surgical termination is recommended to manage medical abortion treatment failures.

- The safety and effectiveness of other mifepristone (Mifeprex) dosing regimens, including use of oral misoprostol tablets intravaginally has not been established by the FDA.
Nesiritide
Recommendations for appropriate use
USA. Nesiritide is indicated for the intravenous treatment of patients with acutely decompensated congestive heart failure who have dyspnoea at rest or with minimal activity. Recently, Scios Inc. has issued a 'Dear Health-care Provider' letter to advise of recommendations on nesiritide (Natrecor) made by an expert panel of cardiology and heart failure clinicians. Following a review of available data with respect to questions of worsened renal function and mortality with nesiritide, the panel agreed that:

- the dose-dependent increase in serum creatinine associated with nesiritide indicated renal dysfunction at the doses detailed in the nesiritide (Natrecor) package insert;
- there was no evidence that nesiritide improved renal function;
- there was a trend towards an increased 30-day mortality rate with nesiritide, but that the confidence intervals were too wide and the number of deaths too small to be certain of an increased mortality risk.

The panel also encouraged Scios Inc. to initiate an educational programme to inform physicians about when nesiritide (Natrecor) should and should not be used.

Reference:

Reboxetine
Genitourinary adverse effects
Australia. The Adverse Drug Reactions Advisory Committee (ADRAC) has received 130 adverse drug reaction reports involving reboxetine (Edronax), including 41 reports of genitourinary disorders that developed within 5 weeks of initiating treatment. In 26 reports, patients experienced symptoms that were consistent with urinary obstruction (hesitancy, retention, dribbling post-micturition and reduced urine flow) and, of those, all but six involved male patients. ADRAC has also received 22 reports of male sexual dysfunction, including erectile dysfunction (n = 4), pain or swelling of the external genitalia or testicles (10) and ejaculation disorders (7), and two reports of women with increased libido. Reboxetine is a selective noradrenaline reuptake inhibitor. ADRAC recommends that, soon after commencing reboxetine treatment, patients should be asked about symptoms of sexual dysfunction or urinary obstruction.

Reference:

Statins
Reports of peripheral neuropathy
Australia. The Australian Adverse Drug Reactions Advisory Committee (ADRAC) has received 281 reports of statin-related peripheral nerve disorders: 136 cases were associated with simvastatin (Zocor, Lipex), 108 with atorvastatin (Lipitor), 26 with pravastatin (Pravachol) and 11 with fluvastatin (Lescol, Vastin). The cases included sensory and mixed sensorimotor peripheral nerve disorders, and a statin was the sole suspected drug in 54% of the cases. Time from treatment initiation to neuropathic symptom onset varied from one dose to 4.5 years. ADRAC comments that, although many patients receiving statin therapy are predisposed to peripheral neuropathy, statin withdrawal resulted in recovery in 52% of the cases, and a positive re-challenge was described in some reports. However, ADRAC says that in some cases, neuropathy persisted for months or years after statin withdrawal.

Reference:
WHO Prequalification Project

The World Health Organization (WHO) has reinstated seven antiretroviral medicines manufactured by Ranbaxy Laboratories Ltd., which had previously been removed from the WHO list of prequalified medicines.

Four of the medicines re-listed had been withdrawn by the manufacturer in November 2004, while the other three had been de-listed by WHO in August 2004 when WHO inspections of independent laboratories used by the manufacturer to run bioequivalence studies had revealed practices which did not conform with the international standards required by WHO.

Later, Ranbaxy commissioned different laboratories to carry out new tests on the products' bioequivalence with the originator medicines. Subsequently, WHO ran the full range of quality, safety and efficacy checks on the medicines as well as thorough inspections of the new laboratories. The products and laboratories were all found satisfactory.

In addition to the above re-listing, three new products by Aurobindo Pharma Ltd. have also been added.

The addition of ten medicines will benefit existing AIDS programmes and procurement schemes. The medicines include:

**Ranbaxy Laboratories Ltd. products:**
- Lamivudine 150 mg tablet, bottle (60), blister (10);
- Lamivudine/Stavudine 150 mg/40 mg tablet, bottle (60), blister (10);
- Lamivudine/Stavudine 150 mg/30 mg tablet, bottle (60), blister (10);
- Zidovudine 300 mg tablet, bottle (60), blister (10);
- Lamivudine/Stavudine/Nevirapine 150mg/40mg/200mg tablets, bottle (60);
- Lamivudine/Stavudine/Nevirapine 150mg/30mg/200mg tablets, bottle (60);
- Lamivudine/Zidovudine 150mg/300mg tablets, bottle (60)

**Aurobindo Pharma Ltd. products:**
- Lamivudine 150mg tablets, Bottle (60)
- Lamivudine 300mg tablets, Bottle (60)
- Zidovudine 300mg tablets, Bottle (60)
## Draft Agenda

### Monday 26 September

<table>
<thead>
<tr>
<th>Time</th>
<th>Activity</th>
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<tbody>
<tr>
<td>8:00 - 9:00</td>
<td>Registration</td>
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<tr>
<td>9:00 - 10:30</td>
<td>Official opening &lt;br&gt;  Report from WHO &lt;br&gt; Report from the Uppsala Monitoring Centre &lt;br&gt; Global overview</td>
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<tr>
<td>11:00 - 11:45</td>
<td><strong>Patient Safety</strong> &lt;br&gt; Speech by Sir Liam Donaldson, Chief Medical Officer, United Kingdom and Chair, World Alliance for Patient Safety &lt;br&gt; Title: Patient Safety: A Global Challenge</td>
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<tr>
<td>11:45 - 12:00</td>
<td>Discussion with WHO staff in Patient Safety</td>
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<tr>
<td>12:00 - 13:00</td>
<td>Reporting back from Twenty-seventh Annual Meeting in Dublin</td>
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<tr>
<td>13:00 - 14:00</td>
<td>Lunch</td>
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<tr>
<td>14:00 - 15:00</td>
<td>How WHO classifications systems can serve pharmacovigilance &lt;br&gt; EIP WHO</td>
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<tr>
<td>15:00 - 15:30</td>
<td>Problems of current interest</td>
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<tr>
<td>15:30 - 16:00</td>
<td>Coffee break</td>
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<tr>
<td>16:00 - 17:30</td>
<td><strong>Working groups</strong> &lt;br&gt; Reporting and Learning &lt;br&gt; Developing an International Taxonomy &lt;br&gt; Pharmacovigilance and ICD 11</td>
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### Tuesday 27 September

<table>
<thead>
<tr>
<th>Time</th>
<th>Activity</th>
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<tbody>
<tr>
<td>9:00 - 10:30</td>
<td><strong>Lessons learnt from Rofecoxib</strong> &lt;br&gt; Presentations from EU, FDA, Ghana followed by discussion</td>
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<tr>
<td>10:30 - 11.00</td>
<td>Coffee break</td>
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<tr>
<td>11:00 - 12.30</td>
<td>Problems of current interest</td>
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<tr>
<td>13.30 - 14.30</td>
<td>Panel discussion on Open access to Database - What needs to be Confidential? &lt;br&gt; Dr K. Hartigan-Go, Philippines</td>
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<tr>
<td>14:30 - 16:30</td>
<td><strong>Working groups (including coffee)</strong> &lt;br&gt; How pharmacovigilance centres react to high profile withdrawals; how can they work more effectively?</td>
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<tr>
<td>16:30 - 17:30</td>
<td>Problems of current interest</td>
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</tbody>
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**Wednesday 28 September**

<table>
<thead>
<tr>
<th>Time</th>
<th>Event</th>
<th>Speaker/Organization</th>
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<tbody>
<tr>
<td>09:00 - 10:00</td>
<td>Quality of reports for signal detection</td>
<td>Member of Signal review panel</td>
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<td>Niklas Norén, UMC</td>
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<tr>
<td>10:00 - 10:30</td>
<td>Discussion on ways to improve quality of reports</td>
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<td>10:30 - 11:00</td>
<td>Coffee break</td>
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<tr>
<td>11:00 - 12:00</td>
<td>Vigibase-on-line presentation</td>
<td>Swissmedic</td>
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<tr>
<td>12:00 - 13:00</td>
<td>Problems of current interest</td>
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<tr>
<td>13:00 - 14:00</td>
<td>Lunch</td>
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<tr>
<td>14:00 - 14:30</td>
<td>Update on ICH developments</td>
<td>Regulator from ICH</td>
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<td>14:30 - 15:00</td>
<td>MedDRA-WHO-ART - Proposal from ICH/MSSO</td>
<td>Member of MedDRA MB</td>
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<td>15:00 - 15:30</td>
<td>Presentations from countries still using WHO-ART</td>
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<td>15:30 - 16:00</td>
<td>Coffee</td>
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<tr>
<td>16:00 - 16:30</td>
<td>Demonstration of Vigibase-on-line</td>
<td>Optional</td>
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**Thursday 29 September**

<table>
<thead>
<tr>
<th>Time</th>
<th>Event</th>
<th>Details</th>
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<tbody>
<tr>
<td>09:00 - 10:30</td>
<td><strong>Public Health Programmes</strong></td>
<td>HIV/AIDS, Malaria and TB</td>
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<td>Update on PV in Programmes Panel discussion</td>
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<td><strong>Vaccines</strong> - Result of Questionnaire</td>
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<td>Discussion with WHO staff in HIV/AIDS, RBM and Vaccines</td>
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<td>10:30 - 11:00</td>
<td>Coffee break</td>
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<tr>
<td>11:00 - 12:30</td>
<td><em>Working groups</em></td>
<td>HIV/AIDS</td>
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<td>Malaria</td>
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<td>Vaccines</td>
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<tr>
<td>14:00 - 15:30</td>
<td>Reporting back from working groups</td>
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<tr>
<td>15:30 - 16:00</td>
<td>Coffee break</td>
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<tr>
<td>16:00 - 16:30</td>
<td>Close of meeting</td>
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