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:

Quality Assurance and Safety: Medicines, EDM–HTP
World Health Organization, 1211 Geneva 27, Switzerland
E-mail address: pals@who.int
Fax: +41 22 791 4730

Further information on adverse reactions may be obtained from the WHO Collaborating Centre for International Drug Monitoring, Stora Torget 3, S-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

No. 5, 2004

News & Issues

As always, we bring you the latest on drug safety and regulatory information from around the world, for your information and for any action as Member States consider appropriate. We have also included a report on the workshop that was held recently in South Africa as a first step towards introducing Pharmacovigilance in HIV programmes in some African countries.

The 27th Annual meeting of representatives of countries participating in the WHO Programme for International Drug Monitoring was held in Dublin, Ireland this year. Focused surveillance methods, as a complement to spontaneous adverse drug reaction reporting system was the theme of the meeting. The sessions on drugs of current interest as well as the working group exercises were very interesting and stimulating. The recommendations from the working groups will be published in the next issue of the newsletter.

The WHO Advisory Committee on Safety of Medicinal Products (ACSoMP) had its second meeting in October, in Geneva. New issues as well as action taken on previous recommendations were reviewed. A report from this meeting will be published in a later issue of the newsletter.

Many of our readers have expressed an interest in joining the e-list for the newsletter. We have over 400 names on the list now and are happy to include more. You can join the list by writing your e-mail details to pals@who.int.
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ANTI-DEPRESSANTS
Labels to include enhanced warnings

USA. The United States Food and Drug Administration (US FDA) has issued a statement to say that it "generally supports the recommendations" received from the Psychopharmacologic Drugs and Paediatric Advisory Committees regarding increased suicidality in paediatric patients receiving antidepressants. The FDA are now working to strengthen the warnings on antidepressant labelling and to increase the information provided to patients. The Advisory Committees concluded that all antidepressants studied in controlled clinical trials increased the risk of suicidal thoughts and actions in paediatric patients, and that any related warning should be applied to all antidepressants, including those that had not been studied in children. The committees thought that access to antidepressants for paediatric patients who may benefit was important; therefore, they did not recommend that the drugs be contraindicated in the US. However, they did recommend that antidepressant labelling include the results of controlled trials of the drugs in children with depression.


ARISTOLOCHIC ACID
To be replaced by Stephania tetrandra and Inula helenium

People's Republic of China. China's State FDA (SFDA) has banned two commonly used herbs containing aristolochic acid, a toxin reported to be linked to kidney failure and cancer. Manufacturers have been directed to replace Aristolochia fangchi and Aristolochia debilis with Stephania tetrandra and Inula helenium respectively, in their traditional medicine formulations by 30 September. The Provincial Drug Bureaux has been instructed to carry out inspections to ensure compliance with the ban by 31 October. Medicines found to contain either Aristolochia fangchi or Aristolochia debilis after 30 September will be treated as fake under Chinese law. By a previous order, special restrictions were imposed on four other potentially harmful aristolochic acid-containing herbs (Fructus Aristolochiae, Aristolochia mollissima Hance, Herba Aristolochiae and Aristolochia tuberose) in China; there was no outright ban on these products. Several countries withdrew aristolochic acid-containing preparations in 1981 following the demonstration of a carcinogenic potential in a three-month toxicity study in rats (see UN Consolidated List of Products whose consumption and/or sale have been banned, withdrawn, severely restricted or not approved by governments, Eighth Issue, Pharmaceuticals, available at http://www.un.org/esa/coordination/ecosoc/Consolidated.List.of.Products.final.pdf).

More recently, in 2001, severe adverse events among users of herbal and dietary preparations containing aristolochic acid have led to bans or consumer warnings in different parts of the world (see WHO's Pharmaceuticals: restrictions in use and availability, April 2003, available at http://www.who.int/medicines/library/docs/en/ from A to z.shtml#p).


ENOXAPARIN
Dosage adjustment needed in patients with renal impairment

USA. Aventis has issued a "Dear Healthcare Professional" letter advising of recent changes to enoxaparin sodium (Lovenox) prescribing information. The letter, sent out in March, was posted on the US FDA website on 17 August 2004. In the "Pharmacokinetics" section, information regarding the clearance and elimination of enoxaparin sodium in obese and low-weight patients, patients with renal impairment and patients on haemodialysis has been clarified, and new information has been incorporated regarding the distribution, metabolism and elimination of enoxaparin sodium in healthy volunteers. In addition, a "Special Populations" section has been added, with subsections for renal impairment, haemodialysis, gender, geriatric and weight considerations. The "Precautions" section has been revised, with a recommendation for dosage adjustment in patients with severe renal impairment (creatinine clearance < 30 mL/min) who have increased exposure to enoxaparin. In patients with mild or moderate renal impairment and in low-weight patients, no specific dosage adjustment is required, but careful observation for signs and symptoms of bleeding in low-weight patients is recommended. Finally, a table has been added to the "Dosage and Administration" section to clarify the recommended treatment and prophylaxis dosage regimens for patients with severe renal impairment.

**INFLIXIMAB**

**Label to reflect haematological and neurological events**

**USA.** Centocor has issued a ‘Dear Healthcare Professional’ letter advising of changes to the USA infliximab (Remicade) label, following post-marketing reports of haematological and neurological events. A ‘Warning on Haematological Events’ has been added to the label to advise of reports of neutropenia, leukopenia, thrombocytopenia and pancytopenia, some of which were fatal. The ‘Warning on Neurological Events’ has also been updated to detail cases of Central Nervous System (CNS) manifestation of systemic vasculitis. In addition, pericardial effusion, neutropenia, and cutaneous and systemic vasculitis have been added to the ‘Adverse Reaction’ sections of infliximab prescribing information. Physicians are advised that they should consider discontinuation of infliximab in patients who develop significant adverse CNS reactions or haematological abnormalities. Infliximab is a biological therapeutic product indicated in the treatment of rheumatoid arthritis and Crohn’s disease.

*Reference:*
Available on the Internet at www.fda.gov

**LEVOTHYROXINE**

**Changes to regulatory status**

**Canada.** Health Canada's Therapeutic Products Directorate (TPD) has issued a notice to manufacturers advising that products containing levothyroxine sodium or digoxin will now be regulated as new drugs, in order to ensure that products are “adequately assessed at the pre-approval stage and appropriately monitored throughout their life-cycle on the market”. The move follows an evaluation of these drugs by the TPD, which determined that levothyroxine and digoxin possess characteristics that could lead to “serious therapeutic failures and/or adverse drug reactions”, if not properly managed.

Meanwhile, in the United States of America, the American Thyroid Association (ATA) Alliance for Thyroid Protection Education has issued a press release to warn patients who take levothyroxine not to change their brand of medication without consulting their physician, following a decision by the US FDA to approve generics as equivalent to branded levothyroxine preparations. The ATA Alliance expresses concern over the methodology that the US FDA has used to determine bioequivalence, and the fact that the decision was made without input from clinical endocrinologists. They also advise that levothyroxine has a narrow toxic to therapeutic ratio, and that excessive or inadequate levels of the hormone could have significant clinical consequences.

*Reference:*

**PHU CHEE/ LIN CHEE/ ACTIVE RHEUMA PLUS**

**Banned due to presence of undeclared glucocorticoids**

**Norway.** The Norwegian Medicines Agency (NoMA) has banned the sale of two herbal medicines, Phu Chee and Lin Chee/Active Rheuma plus, that were found to contain high doses of undeclared dexamethasone (Phu Chee) and prednisolone (Lin Chee/Active Rheuma plus). NoMA has received reports of serious adverse reactions to these herbal medicines. Physicians from a hospital in northern Norway have reported that several patients receiving Phu Chee or Lin Chee/Active Rheuma plus developed symptoms similar to those observed with prolonged use, or high doses, of glucocorticoids, along with subsequent withdrawal symptoms. Laboratory analysis has shown that Phu Chee contains dexamethasone 0.4–0.5mg per tablet and Lin Chee/Active Rheuma plus contains an unknown quantity of prednisolone. As the recommended dosage of Phu Chee was 3–9 tablets/day, patients could have been exposed to a daily dexamethasone dose of 1.2–4.5mg. The number of patients who have taken these drugs is unknown, but over the last two years, they have been mostly used by patients with rheumatoid arthritis and arthrosis. NoMA has sent a letter to all of the distributors’ customers, with warnings about use and rapid discontinuation of the herbal medicines, as well as advice to see a doctor.

*Reference:*

**PHENYLPROPANOLAMINE**

**Banned in the Republic of Korea**

**The Republic of Korea.** On 1 August, 2004, the Korean Food and Drug Administration (KFDA) banned the production and sale of about 170 prescription and over-the-counter cold remedies containing phenylpropanolamine (PPA). The ban follows the conclusions of a Korean study that PPA-containing drugs may be associated with strokes. PPA-containing products were withdrawn in several countries following the publication of an
REGULATORY MATTERS

article (New England Journal of Medicine, 2000; 343: 1826-32) that reported a risk of haemorrhagic stroke associated with the use of PPA. (Also see WHO Pharmaceuticals Newsletter No. 4, 1996).


RIFAMPICIN/ PYRAZINAMIDE

Revised advice

France. Revised recommendations on the use of combination rifampicin and pyrazinamide for latent tuberculosis in patients receiving infliximab (Remicade) have been issued by the French regulatory authority, l’Agence Française de Sécurité Sanitaire des Produits de Santé (AFSSAPS), following reports of cases of serious and sometimes fatal hepatitis. AFSSAPS advises that the combination of rifampicin and pyrazinamide should be avoided and that the combination of rifampicin and isoniazid be used instead or, alternatively, isoniazid alone in elderly patients, in patients with cirrhosis or in the event of toxicity.


ZIPRASIDONE

Updated prescribing information

USA. Pfizer has issued a ‘Dear Healthcare Practitioner’ letter advising of changes to the US prescribing information for ziprasidone (Geodon). The changes, which were made in accordance with a request by the US FDA, warn of an increased risk of hyperglycaemia and diabetes mellitus associated with atypical antipsychotics. The new warning acknowledges reports of hyperglycaemia associated with atypical antipsychotics, and recommends monitoring for symptoms of hyperglycaemia in all patients receiving atypical antipsychotics, including ziprasidone. However, the letter notes that ziprasidone was not included in the epidemiological studies that suggested an increased risk of hyperglycaemia in patients receiving atypical antipsychotics, and that there have been few reports of hyperglycaemia or diabetes associated with the agent. The letter points out that fewer patients have received ziprasidone treatment, and it is not known if this limited experience is the reason for the small number of such reports. The new prescribing information recommends fasting blood glucose testing for patients who develop symptoms of hyperglycaemia during ziprasidone treatment and patients with risk factors for diabetes mellitus, and regular monitoring for worsening glucose control in patients with an existing diagnosis of diabetes mellitus.

BEVACIZUMAB
Increased risk of thromboembolic events

USA. Bevacizumab (Avastin), used in combination with intravenous 5-fluorouracil-based chemotherapy, is indicated for first-line treatment of patients with metastatic carcinoma of the colon or rectum. Recently Genentech Inc. issued a 'Dear Healthcare Provider' letter warning of an increased risk of serious arterial thromboembolic events associated with bevacizumab (Avastin). In the letter, Genentech notes that there is evidence of an association between bevacizumab use and an increased risk of stroke, transient ischaemic attacks, myocardial infarction, angina, and fatal arterial thrombotic events. They advise that patients who experience an arterial thromboembolic event during bevacizumab treatment should discontinue the drug permanently. Genentech is currently revising the package insert for bevacizumab (Avastin) to include detailed information regarding arterial thromboembolic events.

Reference:

CLOPIDOGREL
Reports of haemorrhagic events

Australia. The Australian Adverse Drug Reactions Advisory Committee (ADRAC) warns prescribers of the risk of haemorrhagic events with clopidogrel (Plavix, Isocover), especially when given in combination with other drugs known to cause bleeding. ADRAC has received 460 adverse drug reaction reports associated with clopidogrel, and a total of 130 reports (28%) described haemorrhagic events, 18 of which were fatal. These included patients who received clopidogrel alone (n = 27), in combination with aspirin (27), or with one (25) or two or more (63) anticoagulants, thrombolytics, platelet inhibitors or NSAIDs. In addition, ADRAC has received 80 reports of blood dyscrasias, including one report of thrombotic thrombocytopenic purpura, involving disseminated platelet aggregation. Allergic cutaneous reactions have also been reported in association with clopidogrel (141 reports to ADRAC). Clopidogrel is an anti-platelet agent used for the reduction of atherosclerotic events.

Reference:
Reports in WHO-file:
Purpura thrombopenic thrombotic 46

LAMOTRIGINE
Interaction with hormonal contraceptives

Canada. GlaxoSmithKline Inc, in consultation with Health Canada, has issued a 'Dear Healthcare Professional' letter with the following safety information for the antiepileptic drug, lamotrigine (Lamictal):

- A recent study has demonstrated that concomitant use of hormonal contraceptives with lamotrigine may significantly decrease serum lamotrigine levels.
- GSK has received a limited number of post-marketing reports of break-through seizures, unexpected pregnancies and of menstrual bleeding disorders occurring with the concomitant use of lamotrigine and hormonal preparations.
- Dose adjustments may be needed to counter the interactive effects on serum drug levels. A maintenance dose of lamotrigine may need to be increased by as much as two-fold in women starting or currently taking oral contraceptives and who are not also taking carbamazepine, phenytoin, phenobarbital, primidone or rifampin. On the other hand, the maintenance dose of lamotrigine may need to be decreased by as much as 50% if oral contraceptives are stopped in patients who are not also taking carbamazepine, phenytoin, pheno-barbital, primidone or rifampin.
- Women patients currently being treated with lamotrigine should be advised not to start or stop their oral contraceptives without consulting their physician.
- Although not formally evaluated, similar adjustments may be needed for women receiving lamotrigine in combination with hormonal contraceptives or hormonal replacement therapy.
- Women receiving lamotrigine along with oral contraceptives or other hormonal preparations should notify their physician immediately if they experience changes in their menstrual pattern.

Reference:

NITRO-FURANTOIN
Risk of lung toxicity with long-term use

Australia. Of the 576 reports of suspected adverse drug reactions to nitrofurantoin (Macrodantin, Furadantin, Ralodantin) received by the Australian Adverse Drug Reactions Advisory Committee (ADRAC), 142 (25%) reports described pulmonary toxicity, 40 of which were associated with long-term use of the drug. The reports of pulmonary toxicity...
with long-term use of nitrofurantoin were consistent with interstitial pneumonitis or pulmonary fibrosis and commonly had presenting symptoms of dyspnoea or cough, although some hypersensitivity symptoms were also reported. The ratio of females to males was 7:1, the median age was 70 years (range 47–90), the doses used were 50–300 mg/day and the longest time to onset was 16 years. Of the 40 reports, two patients died after developing pulmonary toxicity and 12 had recovered at the time of reporting. Some reports described indications of persistent lung damage. The ADRAC advises that the risk of pulmonary toxicity should be considered when nitrofurantoin treatment is extended for ≥ 6 months, especially in elderly patients, and that nitrofurantoin should be discontinued if pulmonary symptoms occur.

Reports in WHO-file: Respiratory system disorders 3178


RITUXIMAB
Possible association with Hepatitis B reactivation

Canada. Hoffman-La Roche Limited has issued a 'Dear Healthcare Professional' letter advising of a possible association between rituximab (Rituxan) and hepatitis B virus (HBV) reactivation. The letter is based on recent post-marketing and clinical safety reports, and follows discussions with Health Canada. Cases of HBV reactivation (< 1 per 10 000 patients treated) have been reported in patients receiving rituximab for non-Hodgkin’s lymphoma, usually in combination with antineoplastics, including one report in a Canadian patient. In most cases, hepatitis was diagnosed approximately four months after the initiation of rituximab therapy, and approximately one month after administration of the last dose; fulminant hepatitis, liver failure and death were reported in some patients. The letter advises that patients at high risk of HBV infection should be screened before starting rituximab therapy, and that both HBV carriers and patients who have recovered from HBV infection should be closely monitored during, and up to one year after rituximab therapy. It is suggested that rituximab, and any concomitant anti-neoplastic therapy, be discontinued in patients who develop HBV reactivation.


SELECTIVE SEROTONIN REUPTAKE INHIBITORS (SSRIs)
Potential adverse effects in neonates

Canada. Health Canada has issued an advisory highlighting potential adverse effects of SSRIs and other newer antidepressants in neonates following in utero exposure. This advisory, which applies to bupropion, citalopram, fluoxetine, fluvoxamine, mirtazapine, paroxetine, sertraline and venlafaxine, is intended to increase awareness of the symptoms that may appear in neonates exposed to SSRIs and other newer antidepressants during the third trimester of pregnancy. Health Canada points out that reports of complications at birth requiring prolonged hospitalization, breathing support and tube feeding have been received both in Canada and internationally, with symptoms consistent with either a direct adverse effect, or possibly a discontinuation syndrome.

Patients are warned against stopping their medication without consultation, and are advised to discuss treatment options with their doctor (see WHO Pharmaceuticals Newsletter No. 4, 2004, for related information from the US FDA).


WARFARIN
Interaction with fluoroquinolones

Canada. A total of 57 reports of suspected coagulation disorders associated with concomitant fluoroquinolone and warfarin treatment had been received by Health Canada as of 15 January this year (see table for details). In these 57 reports, 46 patients were aged ≥ 60 years and six were aged < 60 years, with age not reported in the remaining five cases. Forty-nine of the reports were considered to be serious, 16 involved adverse reactions which led to hospital admission and four patients, aged 70–90 years, died. In these reports, values of International Normalized Ratio or INR values as high as 50 were reported and, in 15 of the reports, INR had been stabilized with warfarin before the addition of the fluoroquinolone. Health Canada notes that the interaction is labelled in the official Canadian product monographs for these drugs and that the prothrombin time and INR should be monitored closely, especially in elderly patients, with the anticoagulant dose adjusted accordingly.


Available on the Internet at www.hc-sc.gc.ca
Health Canada reports of coagulation disorders with warfarin/fluoroquinolones

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WARFARIN
Interaction with tramadol

Australia. The Australian Adverse Drug Reactions Advisory Committee (ADRAC) has received 11 reports of an interaction between warfarin and tramadol, resulting in a haemorrhagic event or an increase in INR for blood coagulation time, including two patients who died of haemorrhagic stroke. The median time to onset after the addition of tramadol (Tramal, Zydol) to stabilized warfarin (Coumadin, Marevan) therapy was four days (range 3–7), with the exception of one patient who had an onset time of six weeks. In five of the reports, the patients recovered within 1–4 days of tramadol withdrawal, with or without a reduction in their warfarin dose. The Australian Adverse Drug Reactions Advisory Committee (ADRAC) has advised that, although the interaction appears to be an uncommon event, prescribers should monitor INR for up to a week after adding tramadol to warfarin therapy.

**CYCLO-OXYGENASE - 2 INHIBITORS**

On 30 September Merck & Co., Inc. announced a voluntary withdrawal of rofecoxib (Vioxx) from the United States and worldwide market due to safety concerns of an increased risk of cardiovascular events (including heart attack and stroke) in patients on rofecoxib. Rofecoxib is a prescription cyclooxygenase-2 (COX-2) selective, non-steroidal anti-inflammatory drug (NSAID) that was approved by the US FDA in May 1999 for the relief of the signs and symptoms of osteoarthritis, for the management of acute pain in adults, and for the treatment of menstrual symptoms, and was later approved for the relief of the signs and symptoms of rheumatoid arthritis in adults and children.

Merck withdrew rofecoxib (Vioxx) from the market following the recommendations of the data safety monitoring board overseeing a long-term study in patients at risk of developing recurrent colon polyps. This study was halted because of an increased risk of serious cardiovascular events, including heart attacks and strokes, among study patients taking rofecoxib compared with patients receiving placebo.

The rofecoxib market-withdrawal announcement has come more than five years after the launch of the product in 1999, when more than 80 million patients have already used this medicine, with the annual company sales topping US $ 2.5 billion.

The first trial which showed the association of COX-2 inhibitors with cardiovascular events came as a surprise result from the Vioxx Gastrointestinal Outcomes Research (VIGOR) study in 2000 in which 0.4% of the rofecoxib group and 0.1% of the naproxen group developed myocardial infarction. This result was extended by a between-study comparison conducted by Mukherjee et al. The comparison, which included celecoxib and rofecoxib, implicated both medicines as being associated with a significantly higher rate of myocardial infarction than placebo. The authors postulated that COX-2 inhibitors may have a prothrombotic effect through inhibition of prostacyclin and concluded that 'it is mandatory to conduct a trial specifically assessing cardiovascular risk and benefit of these agents'.

Such a specific trial, however, was never conducted. While the world debates whether the rofecoxib story deserves a full congressional review, it is important, now more than ever, to pay critical attention to the importance of adverse drug reaction (ADR) reporting in a post-marketing set-up and to the 'signal' generating capabilities of the WHO global ADR database.

It is to the credit of the WHO Programme for International Drug Monitoring that the risk of cardiovascular adverse reactions with rofecoxib-use was discussed (in early November 2000, well before the VIGOR study was reported) in the session on 'Drugs of Current Interest', at the 23rd Annual Meeting of Representatives of the National Centres participating in the programme. It was pointed out that within 10 months of its introduction in 2000 in the Netherlands, there were eight reports of cardiovascular problems with four fatalities associated with rofecoxib use; all four cases occurred within four days of commencing therapy and one case occurred two hours after taking the first tablet. It also came to light that there had been one report of a fatality in Malaysia, three reports of cardiac failure in Australia and a total of five reports with various cardiovascular events in Portugal.

COX-2 inhibitors and cardiovascular events were also discussed during the 25th and 27th Annual Meetings of the Programme. Data from the New Zealand Intensive Medicines Monitoring Programme (IMMP) database demonstrated a higher proportion of prothrombotic events and a shorter time to onset of death associated with the use of COX-2 inhibitors than with comparator drugs (that is, all other drugs in the IMMP cohorts for the proportion of prothrombotic events and versus omeprazole in the survival analysis). The only identifiable difference to explain the shorter survival was the higher rate of myocardial infarction and stroke. A cohort of 32 630 patients on celecoxib (mean age 63 years) and 26 666 on rofecoxib (mean age 58 years) was reviewed; ischaemic heart disease was the fourth most common type of event reported for celecoxib and rofecoxib. Of note, there was no difference in rate between the two but celecoxib had twice the rate of cardiac dysrhythmias. Deaths were most commonly represented in the cardiovascular system organ classification for celecoxib and the second most common for rofecoxib.

The WHO Collaborating Centre for International Drug Monitoring uses the BCPNN (Bayesian Confidence Propagation Neural Network) data mining method, to assess disproportionality of a specific ADR-drug combination against the ADR distribution for all drugs in the global ADR database. Of interest is the paper by Zhao et al. who used the BCPNN method to compare the renal-related adverse drug reactions between rofecoxib and celecoxib, from ADR reports in the WHO database at the end of the second quarter of 2000. They concluded that rofecoxib had greater renal toxicity than celecoxib and other traditional NSAIDs; and that, this negative renal impact may have the potential to increase the risk for serious cardiac and/or cerebrovascular events. This paper was published in 2001, nearly three years ahead of the current company withdrawal.
A similar analysis of the WHO global database for celecoxib has also shown an association of myocardial infarction with celecoxib use ('Signal' 2001-09, Restricted document from the WHO Collaborating Centre for International Drug Monitoring). At the time Pharmacia Corporation had responded that it was likely a false-positive association. Sulphonamide reaction terms were reported significantly more frequently with celecoxib compared to rofecoxib in the WHO database (overall sulphonamide relative reporting rate 1.8, 95%CI 1.6-1.9). Amongst these type of reactions, fatal reactions were reported 80% more often (relative reporting rate 1.8, 95%CI 0.9-4.0). These observations, as well as the recent experience with rofecoxib should caution us against dismissing the findings with celecoxib, particularly amidst concerns that the cardiovascular effects of rofecoxib may be a class effect, applicable to all COX-2 selective inhibitors.

References:
WHO training workshop on introducing pharmacovigilance into HIV/AIDS programmes
Pretoria, South Africa
1-10 September 2004

WHO's goal to provide antiretroviral treatment to three million people by 2005 (the 3 by 5 Initiative) means that many countries in Africa will be introducing combinations of antiretrovirals as a policy measure. Some of these drugs are likely to be fixed-dose triple combinations. It is imperative, therefore, that measures should be undertaken to ensure proper monitoring of safety and efficacy of these products in particular.

As with many of the newly registered products there is still limited experience with the operational use of many antiretroviral drugs, especially in the different developing country settings. In particular, there are concerns of safety of these products in the most vulnerable groups (infants and pregnant women) as well in patients with malnutrition and co-morbid conditions including malaria and tuberculosis and in populations where traditional medicines are an integral part of patient care. Unfortunately, most of the countries where these drugs will be used do not have expertise in pharmacovigilance and systems in place for monitoring drug safety. Furthermore, the health care delivery systems will rely on people who may not have the necessary training, knowledge or expertise. In addition, medicine regulatory systems in many of the target countries for upscaling of antiretroviral treatments are not adequately equipped to deal with medicines safety issues.

It was with this background in mind that WHO convened a workshop of HIV/AIDS managers and officials responsible for pharmacovigilance from eight African countries notably Kenya, Malawi, Mozambique, Nigeria, South Africa, Uganda, United Republic of Tanzania and Zambia. A total of 28 participants were exposed to the basic methods and skills for drug safety monitoring, with the aim of introducing a common system of pharmacovigilance of antiretrovirals and where feasible, to initiate large cohort studies to collect data.

The curriculum of the “International training course on pharmacovigilance” developed and regularly conducted by the Uppsala Monitoring Centre was adapted to provide the core introductory course. This was supplemented by material from the Copenhagen HIV programme, one of whose aims is to conduct research into the adverse events arising from antiretroviral therapy using large international multi-centre cohort studies. The training workshop was designed by the Department of Essential Drugs and Medicines Policy, (WHO/EDM) in close collaboration with the WHO Collaborating Centre for International Drug Monitoring (Uppsala Monitoring Centre, the UMC). The following individuals were actively engaged in the planning and teaching activities: Professor I.R. Edwards, UMC, Mr S. Olsson, UMC, Mr Bruce Hugman, UMC, Dr Jens Lundgren, Copenhagen HIV programme, Dr L. Morfeldt, Sweden. Guest speakers were Dr R. Jobson, South Africa and Dr F. Venter, South Africa. The following WHO Secretariat provided facilitation: Dr M. Couper, WHO/EDM, and Ms C. Mullen, WHO/EDM. Dr W. Shasha of the WHO Liaison Office in South Africa and Mr M. Auton in the SADAP (South Africa Drug Action Programme) provided additional support. Overall support from the South Africa Medicines Control Council helped to make the workshop successful.

Each of the eight participating countries developed draft guidelines and plans of action for pharmacovigilance which will be presented to the Ministry of Health of the respective countries. WHO will provide technical support to countries for early implementation, monitoring and evaluation.

**Next steps:**

1. An electronic discussion group for the participants will be established.
2. A consultant will be recruited to carry out follow-up activities in the more advanced countries.
3. Technical assistance will be provided to countries on request for the development of cohort studies.
4. A follow-up meeting to discuss progress is planned for early 2005.
5. Professor I.R. Edwards and Dr J. Lundgren will be invited to WHO to discuss the programme with officials in the HIV/AIDS programme.