WHO PHARMACEUTICALS NEWSLETTER

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

No. 2, 2005

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, PSM–HTP
World Health Organization,
1211 Geneva 27, Switzerland
E-mail address: pals@who.int

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

Contents

Regulatory matters
Safety of medicines
Drugs of current interest
Feature

Issues around best pharmacovigilance practices and crisis management continue to occupy us even as the medical world struggles to understand the full picture with drugs such as the coxibs. Rofecoxib was withdrawn worldwide in September 2004 and in April 2005, the United States Food and Drug Administration asked Pfizer to voluntarily withdraw valdecoxib from the market. Several regulatory agencies have responded by issuing safety information and prescribing guidelines for various COX-2 inhibitors and these are presented in this edition.

The UN Prequalification Project was launched in 2001 for providing quality assessment on a selected number of medicines for high impact diseases that are considered for purchase by several UN agencies. We have included an overview of the team's work under 'Feature' and regular updates of products which have been prequalified by WHO will appear in future issues of the Newsletter.

The World Health Assembly will take place this year from 16 to 25 May, in Geneva. The WHO Collaborating Centre for International Drug Monitoring is holding its biennial training course on Pharmacovigilance from 23 May to 3 June in Uppsala, Sweden. For those of you who will attend either of these events, we hope they will provide opportunities and incentives for promoting health care and pharmacovigilance in your countries.

TABLE OF CONTENTS

Regulatory Matters

Adalimumab -- Updated information on haematologic events 1
Amphetamine -- Anti-ADHD preparations removed 1
Anagrelide -- Contraindicated in patients with severe hepatic impairment 1
Ezetimebe -- Risk of myalgia, rhabdomyolysis, hepatitis, pancreatitis and thrombocytopenia 1
Interferon Beta-1a -- Label updated with hepatic injury information 2
Lipiocis -- Reports of interstitial pneumopathy 2
Natalizumab -- Withdrawn due to serious adverse events 2
Olanzapine -- Medication errors alert 2
Pimecrolimus/Tacrolimus -- Potential cancer risk 3
Promethazine -- Contraindicated in patients less than two years of age 3
Qing zhisan tain shou, Li Da Dai Dai Hua, Meizitang -- Presence of sibutramine 3
Rosuvastatin -- Label to provide risk information in Asian patients 3
Statins -- Moved to pregnancy Category D 4
Valdecoxib - Voluntary removal advised 4

Safety of Medicines

Alimemazine - Paracetamol teething mixture -- Contraindicated in children below two years 5
Amiodarone -- Prescribers advised to be vigilant for serious adverse reactions 5
Aripiprazole -- Increases stroke risk among elderly dementia patients 5
Ayurvedic Medicines -- High levels of heavy metals in some preparations 5
Cyclooxygenase (COX)-2 Inhibitors -- Updated information 6
Drotrecogin alfa (activated) -- Mortality in patients with single organ dysfunction and recent surgery 7
Galantamine -- Additional safety assessment undertaken 8
Methotrexate -- Fatal adverse effects reported 8
Pergolide -- Reports of valvular heart disease 8
Rifampicin -- Interaction with ritonavir-boosted saquinavir 8
Tamoxifen -- Increases risk of fatty liver disease in overweight women 9
Telithromycin -- Adverse reactions update 9
Tenofovir, Didanosine -- New data on adverse events; co-administration not recommended in any ARV combination 9
Tiagabine -- Seizures following off-label use 10

Drugs of Current Interest

Implantable progestogen contraceptives: monitoring for unintended pregnancies 11
An overview of visual side effects associated with erectile dysfunction agents 13

Feature

WHO and its drug Prequalification Project: an overview 15

Adalimumab

Updated information on haematologic events

Canada. Abbott Laboratories Limited has issued a 'Dear Health-care Professional' letter to advise of the addition of new safety information to the adalimumab (Humira, a monoclonal antibody directed against tumor necrosis factor-a) prescribing information, endorsed by Health Canada. The new safety information will also be included in the revised Canadian Product Monograph. Abbott highlights that there have been reports of serious blood dyscrasias, including leukopenia, pancytopenia and thrombocytopenia, in patients receiving adalimumab (Humira). It is not clear whether there is a causal relationship with adalimumab, and none of the reports was received in Canada. Abbott also recommends against the use of adalimumab (Humira) in combination with anakinra (an interleukin-1 antagonist), as there is a risk of severe infections. This advice stems from the observation of serious infections in patients who received anakinra concurrently with another tumour necrosis factor antagonist in clinical studies.

Reference:
'Dear Health-care Professional' letter from Abbott Laboratories Limited, 2 February 2005. Available on the internet at www.hc-sc.gc.ca

Amphetamine

Anti-ADHD preparations removed

Canada. Health Canada has suspended the marketing of amphetamine preparations (Adderall, Adderall XR) used in Attention Deficit Hyperactivity Disorder (ADHD). This directive, which came into effect on 9 February 2005 is based on 20 international reports of sudden deaths in paediatric and adult patients in association with amphetamine (Adderall, Adderall XR) use. These deaths were not associated with overdose, misuse or abuse. Fourteen deaths occurred in children, and six deaths in adults. There were 12 reports of strokes, two of which occurred in children. Health Canada is advising patients who are currently being treated with an amphetamine preparation to consult their physician immediately about use of the drug and about treatment alternatives. Health Canada is also advising that patients who are taking other drugs of the same class for the management of ADHD should not discontinue their medication but should consult their physician if they have queries or concerns. Health Canada has solicited worldwide safety data from manufacturers of other related stimulants used in the treatment of ADHD.

Reference:
Health Canada Warnings/ Advisories, 9 February 2005. Available on the internet at www.hc-sc.gc.ca

Anagrelide

Contraindicated in patients with severe hepatic impairment

USA. Shire Development Inc. is updating the prescribing information for anagrelide (Agrylin), a medication approved in the treatment of thrombocytopenia secondary to myeloproliferative disorders to reduce platelet count and the risk of thrombosis and to ameliorate associated symptoms including thrombo-haemorrhagic events. The new information advises prescribers

i. against using the product in patients with severe hepatic impairment, and

ii. to reduce the dose in patients with moderate hepatic impairment.

The revision follows pharmacokinetic studies that revealed an eight-fold increase in total exposure to anagrelide in patients with moderate hepatic impairment.

Reference:
'Dear Health-care Professional' letter from Shire Development Inc., January 2005. Available on the internet at www.fda.gov

Ezetimebe

Risk of myalgia, rhabdomyolysis, hepatitis, pancreatitis and thrombocytopenia

Canada. Ezetimebe (Ezetrol) is a cholesterol absorption inhibitor that is classified as a systemic drug because of the enterohepatic recirculation of one of its metabolites. Merck Frosst/Schering Pharmaceuticals have updated the product monograph for ezetimebe to include information from international post-marketing reports of rare, and in some cases serious, adverse events associated with ezetimebe use including myalgia, rhabdomyolysis, hepatitis, acute pancreatitis, thrombocytopenia and suspected interaction between ezetimebe and warfarin. The Patient Information section has been updated with signs and symptoms of hepatic, muscle, and pancreatic adverse events for which early consultation with a physician is recommended. Physicians are advised to monitor closely for adverse muscle events in all those patients who have a history of statin intolerance, to consider the diagnosis of pancreatitis in patients who develop sudden acute abdominal pain during therapy with ezetimebe and to monitor liver function before beginning ezetimebe therapy in patients being or about to be treated

with a statin; ezetimebe, in combination with a statin is contraindicated in patients with active liver disease or unexplained persistent elevations of liver transaminases. Additional International Normalized Ratio (INR) measurements are recommended in patients treated with warfarin, and in whom ezetimebe is initiated.

Reference:
'Dear Health-care Professional' letter from Merck Frosst/Schering Pharmaceuticals, 1 February 2005. Available on the internet at www.hc-sc.gc.ca

Interferon Beta-1a

Label updated with hepatic injury information

USA. Post-marketing data on Interferon Beta-1a (Avonex) show that severe hepatic injury, including hepatic failure and elevated serum hepatic enzyme levels, have been reported rarely in patients treated with Interferon Beta-1a (Avonex). In some cases these events have occurred in the presence of other drugs that have been associated with hepatic injury. Health-care professionals are advised that hepatic injury should be considered when Interferon Beta-1a (Avonex) is used in combination with other products associated with hepatic injury, or when new agents are added to the regimen of patients already on Interferon Beta-1a (Avonex). The product information has been updated to reflect the above.

Reference:
'Dear Health-care Professional' letter from Biogen Idec, 16 March 2005. Available on the internet at www.fda.gov

Lipiocis

Reports of interstitial pneumopathy

France. CIS Bio (subsidiary company of the Schering group), in agreement with the French agency for medical safety of health products (AFSSAPS) is informing health professionals that the incidence of interstitial pneumopathy associated with the use of Lipiocis® appears to be higher (2%) than initially observed in clinical trials (0.5%). Lipiocis is a radiopharmaceutical product indicated in the treatment of hepatocellular carcinomas with thrombosis of the portal vein. A total of 13 interstitial cases of pneumopathy have been reported to the French reference centre for the treatment of hepatocellular carcinomas. These diffuse infiltrative pneumopathys occur approximately a month after the injection of Lipiocis®, generally after the second injection. The clinical symptoms include the appearance of dyspnea sometimes associated with a dry cough and bilateral crepitations. The pneumopathys could lead to serious complications with a high death rate. AFSSAPS recommends that thoracic radiography must be carried out before administering Lipiocis® and if respiratory symptoms are observed. The Summary of Product Characteristics has been updated to reflect this information.

References:
1. Letter to health professionals from Dr Laure Udin, Responsible Officer, Pharmacovigilance, AFSSAPS, 14 March 2005. Available on the internet at http://afssaps.sante.fr/htm/10/filltrpsc/lp050304.pdf
2. Modified Summary of Product Characteristics for Lipiocis. Available on the internet at http://afssaps.sante.fr/pdf/10/lipiocis.pdf

Natalizumab

Withdrawn due to serious adverse events

USA. The United States Food and Drug Administration (US FDA) has issued a public health advisory to inform patients and health-care providers that Biogen Idec has voluntarily suspended marketing of natalizumab (Tysabri) due to serious adverse event reports. The company has received two reports, one fatal and one possible case of progressive multifocal leukoencephalopathy in patients enrolled in a clinical trial who had been receiving natalizumab for multiple sclerosis for more than two years. Neither patient had any known risk factors for progressive multifocal leukoencephalopathy. On the basis of these cases, Biogen Idec is suspending dosing of the agent in clinical trials as well as voluntarily suspending marketing. At the present time, the only recommendation for patients receiving natalizumab is to discontinue its use, and for physicians to evaluate all patients who have received the agent and have signs or symptoms suggestive of progressive multifocal leukoencephalopathy.

Reference:
US FDA Public Health Advisory, 28 February 2005. Available on the internet at www.fda.gov

Olanzapine

Medication errors alert

USA. Eli Lilly & Company have issued a `Dear Health-care Professional' letter to advise of dispensing and prescribing error reports with the antipsychotic medication olanzapine (Zyprexa) and the antihistaminic preparation cetirizine (Zyrtec). Dispensing of olanzapine instead of cetirizine or vice versa has led to adverse events in patients. Such a mix-up may result in, for example, a disease relapse

in patients with schizophrenia or bipolar disorder. Factors that may contribute to the medication errors are: the first two letters of their brand names are the same, the products are usually stored near each other, both are available in 5 mg and 10 mg tablets and both have a once-daily dosing interval. Measures that have been or will be taken by Eli Lilly include changing the 10 mg ZYPREXA bottle label to ZyPREXA, for easier identification and, launching an awareness campaign focusing on the dispensing error potential.

Reference:
'Dear Health-care Professional' letter from Eli Lilly & Company, 26 January 2005. Available on the internet at www.fda.gov

Pimecrolimus/ Tacrolimus
Potential cancer risk

USA. The US FDA Division of Paediatric Drug Development has recommended that a black box warning be added to the labeling of two eczema treatments, pimecrolimus (Elidel) and tacrolimus (Protopic), to warn of potential carcinogenicity with these products. This recommendation is based on all available information regarding these agents, including animal carcinogenicity signals in mice and monkeys and post-marketing reports of tumour-related adverse events. The division says available data raise *"serious safety concerns in children regarding the potential for carcinogenicity in humans"* with agents indicated for the treatment of the non-life-threatening condition, atopic dermatitis. In animals, the carcinogenicity signal with the two products is *"strong, consistent, and dependent on dose and treatment duration"*. Furthermore, in humans, there have been a number of post-marketing reports of lymphoma (n = 7), skin cancer (6) and papilloma (2) with these two agents, and the division notes that the increased incidence of specific infections with pimecrolimus (Elidel) and tacrolimus (Protopic) in clinical trials provides *"additional supportive evidence of immunosuppression in paediatric patients"*. The US FDA has advised health-care professionals to prescribe the two products only as directed (minimum dose, for the shortest period of time and never in children younger than two years of age) and only after other eczema treatments have failed to work.

Reference:
US FDA Talk Paper, 10 March 2005. Available on the internet at www.fda.gov

Promethazine
Contraindicated in patients less than two years of age

USA. Wyeth Pharmaceuticals, under advice from the US FDA has updated its labels for promethazine hydrochloride (Phenergan) tablets and suppository preparations. The new labels warn against using these products in children below the age of two due to the risk of fatal respiratory depression. This advice is based on post-marketing reports of respiratory depression including fatalities associated with the use of promethazine hydrochloride preparations in paediatric patients of this age group. Caution is needed when using this product in children two years of age and older. The Contraindications, Warnings/Use in Paediatric Patients and Dosage and Administration sections of the label now reflect the above information.

Reference:
'Dear Health-care Professional' letter from Wyeth Pharmaceuticals, 21 January 2005. Available on the internet at www.fda.gov

Qing zhisan tain shou, Li Da Dai Dai Hua, Meizitang
Presence of sibutramine

UK. The Medicines and Health-care products Regulatory Agency (MHRA) has become aware of the supply of a Traditional Chinese Medicine (TCM) slimming aid called Qing zhisan tain shou on the UK market, which contains the prescription only medicine (POM) sibutramine. The MHRA is warning consumers that sibutramine should only be prescribed under specific circumstances and requires the supervision of a registered doctor as it can cause a rise in blood pressure. Qing zhisan tain shou is supplied in a bicolour cream and brown capsule form. The capsules are contained within blister packs and presented in a white and green carton with various lettering and imagery. Two other TCM slimming products, Li Da Dai Dai Hua and Meizitang have been seized by the Netherlands' authorities and have been found to contain sibutramine. Due to the international trade in such products it is possible that these, or similar products, have found their way onto the UK market and consumers are urged to be vigilant.

Reference:
Herbal Safety News, March 2005. Available on the internet at www.mhra.gov.uk

Rosuvastatin
Label to provide risk information in Asian patients

Canada, USA. The US FDA and Health Canada have issued Public Advisories highlighting

the findings from a phase IV pharmacokinetic study showing increased rosuvastatin (Crestor) concentrations in Asian patients. In the US, the Dosage and Administration section of the labeling for rosuvastatin (Crestor) has been updated on the basis of the results of a phase IV pharmacokinetic study which showed an approximately two-fold increase in rosuvastatin concentrations in Asian Americans compared with Caucasians. This section now states that the 5 mg dose should be considered as the starting dose for Asian patients, and that any increase in dose should take into consideration the increased exposure in this population. The results of this study are also discussed in the Clinical Pharmacology and Precautions sections of the rosuvastatin (Crestor) label. Furthermore, the Warnings section and the Dosage and Administration section have been revised to emphasize, in a bolded paragraph, the risks of myopathy, particularly at the 40 mg dose, and now explicitly state that the 5 mg dose is available as a starting dose for those who do not require aggressive cholesterol lowering or who have predisposing risk factors for myopathy. Health Canada has issued a Public Advisory to advise Canadians of the study findings, and has advised that the 40 mg dose of rosuvastatin (Crestor) should not be used in patients with factors that put them at increased risk for rhabdomyolysis, including Asian ethnicity. Health Canada has also advised that the 5 mg dose is recommended as the starting dose for Asian patients and has asked manufacturers of all statins to update the information in the Canadian Product Monographs to 'enhance the safe and effective use' of these agents.

References:

1. US FDA Public Health Advisory, 2 March 2005. Available on the internet at www.fda.gov

2. 'Dear Health-care Professional' letter from AstraZeneca Canada Inc., 8 March 2005. Available on the internet at www.hc-sc.gc.ca

Statins

Moved to pregnancy Category D

Australia. The pregnancy classification of the statins has been changed from category C to category D by the Australian Drug Evaluation Committee. The classification change for the statins, already contraindicated in pregnancy, comes after publication of a series of cases of fetal malformation. Category D drugs are those "which have caused, are suspected to have caused or may be expected to cause, an increased incidence of human fetal malformations or irreversible damage" and may also have adverse pharmacological effects.

Reference:

Australian Adverse Drug Reactions Bulletin 24: 4, No. 1, February 2005.

Valdecoxib

Voluntary removal advised

USA. The US FDA has asked Pfizer to withdraw valdecoxib (Bextra) from the market because of :

- Lack of adequate data on the cardiovascular safety of long-term use of valdecoxib (Bextra), along with the increased risk of adverse cardiovascular events in short-term coronary artery bypass surgery (CABG) trials;
- reports of serious and potentially life-threatening skin reactions, including deaths, in patients using valdecoxib (Bextra) and,
- lack of any demonstrated advantages for valdecoxib (Bextra) compared with other NSAIDs.

Reference:

Public Health Advisory, 7 April 2005. Available on the internet at www.fda.gov

Alimemazine - Paracetamol teething mixture

Contraindicated in children below two years

UK. The Medicines Healthcare products Regulatory Agency (MHRA) is warning health-care professionals that a teething mixture containing alimemazine tartrate and paracetamol, which contains dosing information for patients over three months of age, is actually contraindicated in children below two years. Health-care professionals are asked to consider this product as a potential cause of adverse effects in any presenting patients, and patients should be advised to destroy any unused portion of the mixture.

Reference:
News & Updates, NHS, 17 February 2005. Available on the internet at www.druginfozone.nhs.uk

Amiodarone

Prescribers advised to be vigilant for serious adverse reactions

New Zealand. Prescribers are advised to be vigilant for serious adverse drug reactions (ADRs) associated with amiodarone (Cordarone X, Aratac) in a Prescriber Update article on New Zealand's Medsafe web site. By the end of December 2004, New Zealand's Centre for Adverse Reactions Monitoring had received 340 reports of ADRs associated with amiodarone; serious ADRs reported include eye, lung, liver, heart and thyroid disorders. Medsafe advises prescribers to conduct baseline lung, liver and thyroid function tests, an ECG, serum potassium levels and an ophthalmological examination before patients start treatment with amiodarone. In addition, Medsafe recommends regular monitoring of patients receiving long-term amiodarone therapy, and continued monitoring of thyroid function for several months after amiodarone discontinuation. Medsafe also advises that patients be informed of the potential symptoms of amiodarone-related ADRs and encouraged to promptly seek medical advice if those symptoms develop.

Reference:
Prescriber update articles, February 2005. Available on the internet at www.medsafe.govt.nz

Aripiprazole

Increases stroke risk among elderly dementia patients

Sweden. The Swedish Medical Products Agency (MPA) has advised that aripiprazole (Abilify) may be associated with an increased risk of cerebrovascular events such as stroke and transient ischaemic attack in elderly patients with dementia. Three clinical studies, in which elderly patients (mean age 84 years) received aripiprazole (n = 595) or placebo (343) for 10 weeks for psychosis associated with Alzheimer's disease, demonstrated an increased risk of cerebrovascular events associated with aripiprazole (n = 8; 1.3%), compared with placebo (2; 0.6%). Bristol-Meyers Squibb is to inform physicians about this data, and the aripiprazole product information is to be updated. The MPA advises that, in Sweden, aripiprazole has not been approved for the treatment of psychosis and/or behavioural disorders associated with dementia, and recommends that patients currently receiving aripiprazole should be re-evaluated in light of these risks.

Reference:
Information from the Swedish Medical Products Agency, 4 February 2005. Available on the internet at www.mpa.se

Ayurvedic Medicines

High levels of heavy metals in some preparations

Canada. Health Canada is warning that according to a study in the United States, as many as 14 ayurvedic preparations have been reported to contain high levels of lead, mercury and/or arsenic. The US study report has been published in the December 2004 issue of the Journal of the American Medical Association, JAMA. Three of the products are suspected to be available in various parts of Canada although none has been authorized for sale in this country.

Ayurvedic medicinal products are used in the traditional Indian healing paradigm. According to the principles of Ayurvedic medicines, heavy metals are used in a detoxified state in these medicinal products because of their reputed therapeutic properties. However, should the detoxification process not be strictly followed during manufacturing, it is possible for the resulting product to contain high levels of heavy metals.

Heavy metals may accumulate in vital organs and thus pose a particular health risk. Arsenic poisoning can affect the liver, bone marrow, cardiovascular and central nervous systems, causing nausea, abdominal pain, vomiting, muscle cramps, heart abnormalities, liver damage, anaemia and reduced motor nerve function. Lead poisoning can affect the kidneys, liver, heart, and central nervous system causing weight loss,

insomnia, dizziness, swelling of the brain and paralysis. Mercury poisoning can affect the kidneys and central nervous system causing tremors, insomnia, memory loss, slowed sensory and motor nerve function and reduced mental function. A full list of the products can be seen at the Warnings and Advisories section of the Health Canada homepage (see reference below). Health Canada is currently determining the availability of the listed products in Canada to ascertain appropriate action. In the meantime, consumers are warned not to use any of these products. Those who have used the preparations in the past and are concerned about their health are advised to consult their physician.

Reference:
Health Canada Warnings/ Advisories, 3 March 2005. Available on the internet at http://hc-sc.gc.ca

Cyclooxygenase (COX)-2 Inhibitors

Updated information

Australia, Europe, India, New Zealand, USA.
Following the withdrawal of rofecoxib in September 2004 on account of an increased risk of myocardial infarction and stroke being demonstrated in a clinical trial, several drug regulatory agencies worldwide have undertaken a full review of all available data on the cardiovascular safety of all cyclooxygenase-2 (COX-2) inhibitors. COX-2 inhibitors belong to a relatively new class of non-steroidal anti-inflammatory medicines used in the treatment of arthritis. In particular, celecoxib, etoricoxib, lumiracoxib, valdecoxib and parecoxib are being investigated. The Australian Therapeutic Goods Administration (TGA), the European Medicines Evaluation Agency (EMEA) and the New Zealand Medicines and Medical Devices Safety Authority (MEDSAFE) have all completed preliminary accelerated reviews of the COX-2 inhibitors and, pending a full review, have announced interim regulatory restrictions on the use of these medicines. Preliminary analyses suggest a class-effect, with an increased risk of cardiovascular adverse events for all COX-2 inhibitors.

Australia[1]:
The Australian Drug Evaluation Committee (ADEC) made a number of recommendations to restrict the use of these drugs in Australia.

The TGA will immediately require manufacturers of COX-2 inhibitors to place new highlighted explicit warnings in product information about the increased risk of adverse cardiovascular events from this group of drugs. The new warning statements are to be highlighted with a black boxed margin.

The TGA is also advising people who are taking more than 200 mg a day of celecoxib (Celebrex) or more than 15 mg a day of meloxicam (Mobic; Movalis) to review their treatment regime with their doctors.

The TGA has also accepted a number of other recommendations of ADEC and has given notice to the relevant companies.

- It is proposed to cancel the registration of the drug parecoxib (Dynastat) because of the risk of cardiovascular events. Dynastat **is marketed in Australia** and is approved as a single dose at the time of surgery to reduce post-operative pain.
- It is proposed to withdraw the indication of management of arthritis of the drug valdecoxib (Valdyne, Dynoral - known in some countries as Bextra) which is converted to parecoxib in the body. Valdecoxib **has not been marketed in Australia.** Valdecoxib has been associated with an increased risk of cardiovascular events in cardiac bypass graft patients. The use of valdecoxib for five days as an analgesic in patients without increased cardiovascular risk will remain.
- It is proposed to greatly limit the approved uses of two other COX-2 inhibitors which **have not yet been marketed in Australia**. They are etoricoxib and lumiracoxib. In both instances, ADEC was not sufficiently assured of the safety of these drugs for anything other than short term use in patients without increased cardiovascular risk.

People who are concerned about their use of COX-2 inhibitors should discuss their treatment with their medical practitioner.

European Medicines Evaluation Agency[2]:
The following urgent safety restrictions have been taken for COX-2 inhibitors available in the European Union.

- A contraindication is introduced for all COX-2 inhibitors in patients with ischaemic heart disease or stroke.
- As a further measure, a contraindication is introduced for etoricoxib in patients with hypertension (high blood pressure) whose blood pressure is not under control.
- A warning is introduced for prescribers to exercise caution when prescribing COX-2 inhibitors for patients with risk factors for heart disease, such as

hypertension, hyperlipidaemia (high cholesterol levels), diabetes and smoking, as well as for patients with peripheral arterial disease.

- Given the association between cardiovascular risk and exposure to COX-2 inhibitors, doctors are advised to use the lowest effective dose for the shortest possible duration of treatment.

These are interim measures pending the finalization of the class review. The Agency's Committee for Medicinal Products for Human Use (CHMP) also concluded that more research is needed in the field to evaluate the cardiovascular safety of COX-2 inhibitors, and that ongoing cardiovascular trials should continue as planned.

Pfizer Inc. has issued an updated Summary of Product Characteristics (SPCs) for celecoxib (Celebrex), valdecoxib (Bextra) and parecoxib (Dynastat) in light of recent EMEA guidance on COX 2 inhibitors. These agents are now contra-indicated in patients with:

- Ischaemic heart disease
- Cerebrovascular disease
- Class II-IV congestive heart failure

The company advises that patients with significant risk factors for cardiovascular events (e.g., hypertension, hyperlipidaemia, diabetes mellitus, smoking) or peripheral arterial disease should only be treated with these drugs after careful consideration. Pareoxib and valdecoxib should not be used in the treatment of post-operative pain following coronary artery bypass graft (CABG). Other treatment options should be considered in the absence of increased therapeutic benefit from a dose increase in celecoxib and valdecoxib.

New Zealand[3]:

The Ministry of Health advises that anyone taking a COX-2 inhibitor should follow the advice provided by the Ministry's expert committee, released in December last year, that COX-2 agents are not recommended:

- for routine use in patients with rheumatoid arthritis or osteoarthritis except where the patient is at "high risk" of developing a serious gastrointestinal adverse effect from other standard non-steroidal anti-inflammatory agents;
- for patients at high risk of heart attack or stroke;
- for patients already taking aspirin;
- for routine relief of post-operative pain.

Patients already taking COX-2 inhibitors on a regular basis should discuss the continuing use of these medicines with their general practitioner or specialist. Prescribers should discuss with their patients the available alternatives, and review the risks and benefits of these alternatives compared with the emerging clinical concerns about the COX-2 inhibitors, before deciding on the best course of treatment for that individual. If the patient and prescriber decide that continued use of a COX-2 inhibitor is appropriate, use of the lowest effective dose is prudent.

USA[4]:

- After three days of deliberations, an advisory panel to the US FDA decided that the widely used COX-2 inhibitors rofecoxib, celecoxib and valdecoxib all carry serious risks of heart attack and stroke. The panel recommended that these products should carry strongly worded 'black box' warnings about these risks.

A WHO Information Exchange note was issued summarizing actions/statements from various countries.[5]

India[6]:

The Indian National Pharmacovigilance Advisory Committee has recommended that selective COX-2 inhibitors such as celecoxib, valdecoxib, parecoxib as well etoricoxib should carry a 'precautionary warning' on their label saying that they should be used with caution in patients suffering from coronary heart disease/cardiovascular disorder. The committee had earlier recommended that the use of all rofecoxib products should be discontinued in India.

References:

1. TGA Media Statement, 10 February 2005. Available on the internet at http://www.tga.gov.au
2. EMEA Public Statement, EMEA/62838/2005, 17 February 2005. Available on the internet at http://www.emea.eu.int
3. MEDSAFE Alert/Letter, 22 February 2005. Available on the internet at http://www.medsafe.govt.nz
4. British Medical Journal, 26 February 2005; 333:440.
5. Cyclooxygenase-2 inhibitor medicines. QSM/MC/IEA.111, WHO Information Exchange System, 28 February 2005.
6. Scrip World Pharmaceutical News No. 3025, 2 February 2005; pg 18.

Drotrecogin alfa (activated)

Mortality in patients with single organ dysfunction and recent surgery

Canada, USA. Eli Lilly Inc. and Company have some new information for health professionals regarding the use of drotrecogin alfa (activated) (Xigris), indicated for the treatment of adult patients with severe sepsis (sepsis associated

with acute organ dysfunction) who have a high risk of death. According to Eli Lilly, patients with single organ dysfunction and recent surgery may not be at high risk of death and therefore may not be indicated for drotrecogin alfa (activated) treatment. In two recent trials using drotrecogin alfa (activated), a higher mortality was observed in patients treated with drotrecogin alfa as compared to placebo. While a definitive explanation is not available, these deaths underscore the importance of accurate severe sepsis diagnosis and assessment of risk of death when considering patients for drotrecogin alfa therapy.

Reference:

1. Letter from Eli Lilly Canada Inc., 31 January 2005. Available on the internet at www.hc-sc.gc.ca

2. 'Dear Health-care Professional' letter from Eli Lilly & Company, January 2005. Available on the internet at www.fda.gov

Galantamine

Additional safety assessment undertaken

The Netherlands. The Medicines Evaluation Board (MEB) in the Netherlands is reminding health professionals that galantamine (Reminyl) is not approved in the indication of mild cognitive impairment (MCI) in the Netherlands but only for the treatment of mild to moderate Alzheimer's dementia. The MEB, in co-operation with other European competent authorities has started an additional safety assessment of the drug following the preliminary analyses of data from two international studies that were undertaken to see if the onset of dementia could be delayed in patients with mild cognitive impairment (MCI); a total of 15 patients died in the galantamine treated group and five in the placebo treated groups in these studies. The cause of death varied but was mainly of cardiovascular or cerebrovascular nature. The MEB advises that pending further data, galantamine may not be used outside the approved indications and that patients with Alzheimer's dementia should be treated and followed up according to national recommendations (see WHO Pharmaceuticals Newsletter No.1, 2005 for similar advice from Health Canada).

Reference:

News and Publications, Medicines Evaluation Board, Netherlands, 5 March 2005. Available on the internet at www.cbg-meb.nl

Methotrexate

Fatal adverse effects reported

Japan. Doctors in Japan have reported 831 serious adverse effects associated with methotrexate (Rheumatrex) to Wyeth K.K., between March 1999 and November 2004; 134 reports were of fatal adverse effects, including interstitial pneumonia and myelosuppression. An estimated 100 000 people are taking methotrexate (Rheumatrex) in Japan. Wyeth K.K. has warned doctors and patients that methotrexate (Rheumatrex) is associated with 'life-threatening' and 'sometimes serious' adverse effects, and has requested that the drug be used carefully. However, pharmaceutical experts have demanded that the manufacturer and the government clearly outline the risks associated with methotrexate.

Reference:

Japanese Media Release, 12 February 2005. Available on the internet at www.japantimes.co.jp

Pergolide

Reports of valvular heart disease

Singapore. Three reports of pergolide-associated valvular heart disorders have been received by Singapore's Health Sciences Authority, reports the country's adverse drug reactions news bulletin. The reports involved men aged 55–71 years who had been receiving pergolide for 1.7–5.2 years before they were found to have valvular heart disorders.

Reference:

Adverse Drug Reactions News (Singapore) 6:3, No.3, December 2004.

Rifampicin

Interaction with ritonavir-boosted saquinavir

Canada, USA. Roche Laboratories Inc. in the US and Hoffmann-La Roche Limited in Canada are advising health professionals of an interaction between rifampicin (antituberculosis medication) and ritonavir/saquinavir (used in HIV treatment) which has been associated with hepatitis and marked elevations in aminotransferase levels. Rifampicin is currently contra-indicated for use with saquinavir because of a pharmacokinetic interaction. To investigate whether boosting saquinavir with ritonavir would overcome this interaction, researchers conducted a 28-day, randomized, open-label, multiple-dose study in healthy subjects. A total of 28 subjects received rifampicin 600 mg once daily in combination with ritonavir/saquinavir 100 mg/1000 mg twice daily. Eleven of these subjects (39.3%) developed significant hepatocellular toxicity; in some cases, aminotransferase levels were elevated to more than

twenty times the upper limit of normal, and one subject was hospitalized with marked aminotransferase level elevations. All affected subjects improved following drug discontinuation, and the study was stopped. Roche advises prescribers that they should not administer rifampicin to patients with HIV infection who are also receiving ritonavir/saquinavir as part of combination antiretroviral therapy. The package inserts will soon be revised with this information.

References:
1. 'Dear Health-care Provider' letter from Roche Laboratories Inc., February 2005. Available on the internet at www.fda.gov
2. 'Dear Health-care Professional' letter from Hoffmann-La Roche Limited, 10 February 2005. Available on the internet at www.fda.gov

Tamoxifen

Increases risk of fatty liver disease in overweight women

Italy. Tamoxifen appears to increase the risk of non-alcoholic fatty liver disease, including steatohepatitis, but only among overweight and obese women, according to researchers from Italy. To determine the incidence of, and risk factors for non-alcoholic fatty liver disease associated with tamoxifen, the researchers evaluated a cohort of 5408 women with a history of breast cancer who had undergone hysterectomy and were enrolled in the prospective, multicentre, double-blind Italian tamoxifen chemoprevention trial. The women were randomized to receive tamoxifen 20 mg/day (n = 2708) or placebo (2700) for five years.

Significantly more women in the tamoxifen group met the criteria for suspected non-alcoholic fatty liver disease during treatment than in the placebo group (34 vs 18), but this excess was restricted to the first two years of treatment. The fatty liver disease was confirmed by ultrasonography in all 52 women; in the 20 women who had liver biopsy, steatohepatitis (12 tamoxifen, 3 placebo) and fatty liver (1 tamoxifen, 4 placebo) were confirmed.

On multivariate analysis, tamoxifen was associated with an increased risk of developing suspected non-alcoholic fatty liver disease, with a hazard ratio (HR) of 2 (95% CI 1.1, 3.5). However, this association was restricted to women with a body mass index ≥ 25 (HR 2.3; 1.2, 4.6). Additional factors associated with the development of suspected non-alcoholic fatty liver disease included being overweight (HR 2.4; 1.2, 4.8), obesity (3.6; 1.7, 7.6), hypertension (2; 1, 3.8) and severe baseline hypercholesterolaemia (3.4; 1.4, 7.8).

Reference:
Bruno S, Maisonneuve P, Castellana P, Rotmensz N, Italian Tamoxifen Study Group, et al. Incidence and risk factors for non-alcoholic steatohepatitis: prospective study of 5408 women enrolled in Italian tamoxifen chemoprevention trial. British Medical Journal, March 2005. Available on the internet at http://bmj.bmjjournals.com

Telithromycin

Adverse reactions update

Canada, Japan. Aventis Pharma in Japan has received six reports of syncope in patients receiving telithromycin (Ketek). Aventis Pharma estimates that 2.3 million patients in Japan have taken telithromycin since the drug became available in December 2003. The vendors of telithromycin in Japan (Sankyo Co. and Fujisawa Pharmaceutical Co.) are advising doctors about the possibility of syncope in a warning on the drug instructions and through medical representatives. As of 15 Sept 2004, Health Canada had received 25 reports of suspected adverse reactions to telithromycin since the drug become available on the Canadian market (29 May 2003). Seven of these reports were of suspected interactions between telithromycin and anticoagulants (six with warfarin and one unspecified) leading to increased (n = 6) or decreased (1) INR (International Normalized Ratio) values; INR was known to have been previously stabilized on warfarin in five of the cases. The patients were aged 50–79 years, the change in INR was noted 1–9 days after telithromycin was started, and warfarin and/or telithromycin dose adjustments were required in six of the seven cases.

References:
1. Japanese Media Release, 22 December 2004. Available on the internet at www.morningstar.com
2. Canadian Adverse Reaction Newsletter 15: 1-2, No. 1, January 2005.

Tenofovir, Didanosine

New data on adverse events; co-administration not recommended in any ARV combination

Europe. The European Medicines Evaluation Agency (EMEA) has issued a public statement about the efficacy and safety of tenofovir and didanosine co-administration.[1] The statement refers to new reports of virological failure and emergence of resistance following co-administration of these two medicines as observed in several clinical

studies: tenofovir disoproxil fumarate and didanosine were co-administered with a non-nucleoside reverse transcriptase inhibitor in HIV-infected treatment-naïve adult patients with high baseline viral load and low CD4 cell counts. Similar reports had been previously observed with this dual combination in the context of triple combination therapy with a nucleoside/ nucleotide reverse transcriptase inhibitor and were the subject of recommendations by the EMEA on 22 October 2003.[2] A WHO Drug Alert was also issued on this information.[3] The precise nature of any interaction leading to non-response is still not known. Based on the new clinical data the EMEA notes that :

- The co-administration of tenofovir disoproxil fumarate and didanosine is not recommended within any antiretroviral combination therapy, and particularly in patients with high viral load and low CD4 cell count.
- Rare, sometimes fatal cases of pancreatitis and lactic acidosis have been reported with the co-administration of tenofovir and didanosine.
- If this combination is considered to be strictly necessary, patients should be closely monitored for efficacy and didanosine-related adverse events.

The Product Information for tenofovir disoproxil fumarate (Viread) has now been modified to reflect the above-mentioned information.

References:

1. EMEA Public Statement EMEA/62331/2005, 3 March 2005. Available on the internet at www.emea.eu.int
2. EMEA Public Statement EMEA/CPMP/5094/03, 22 October 2003. Available on the internet at www.emea.eu.int
3. WHO Drug Alert 109, 24 October 2003. Available on the internet at www.who.int/medicines/library/drugalert

Tiagabine

Seizures following off-label use

USA. The US FDA has issued a Public Advisory, and Cephalon has issued a `Dear Health-care Provider' letter, to announce that a Bolded Warning will be added to the tiagabine (Gabitril) label about the risk of new-onset seizures and status epilepticus in patients without epilepsy who receive the drug for off-label indications; tiagabine (Gabitril) should be discontinued in such patients. From 1997 to 31 December 2004, there have been 59 post-marketing reports of seizures in patients without epilepsy receiving the drug; the US FDA has also received several reports of status epilepticus. The seizures typically occurred soon after tiagabine initiation or dose increases, but seizures have been reported with tiagabine (Gabitril) doses as low as 4 mg/day. Most patients were receiving concomitant medications that may have lowered the seizure threshold. Cephalon has also made changes to the Adverse Reactions, Pharmacokinetics, Overdosage and Dosage and Administration sections of the tiagabine (Gabitril) label, and will target health-care professionals and patients with an educational campaign in order to discourage off-label use of the drug.

References:

1. 'Dear Health-care Provider' letter from Cephalon Inc., 14 February 2005. Available on the internet at www.fda.gov
2. US FDA Public Health Advisory, 18 February 2005. Available on the internet at www.fda.gov

Patient reporting of suspected ADRs launched in the UK

Pilot schemes for patient reporting of suspected adverse drug reactions (ADRs) have been launched in the UK. Patients are encouraged to report suspected ADRs to the UK Medicines and Healthcare products Regulatory Agency (MHRA) via paper-based Patient Yellow Card forms or the Yellow Card Scheme web site.

Reference: *www.mhra.gov.uk*

Implantable progestogen contraceptives: monitoring for unintended pregnancies

Globally, contraceptive prevalence has risen from 30% in the 1960s to 61% in 2003 among all women of reproductive age who are married or in a consensual union.[1] This increase has been particularly dramatic in developing countries, rising from 9% to more than 50% in this period. With a growing number of options at their disposal, women make contraceptive decisions that best reflect personal, social and economic circumstances.

Hormone releasing implantable contraceptives are used by increasing numbers of women worldwide. These implants consist of synthetic progestogens in polymer capsules or rods. They are inserted subdermally, under local anaesthesia, usually in the inner aspect of the non-dominant arm. The implants slowly release the progestogen in small amounts that decrease over the life-spans of the implants which vary between six months and five years.

The first scientific publication on a progestogen-releasing contraceptive implant for women appeared in 1969.[2] In 1983 the first levonorgestrel implant, Norplant, was approved by the Finnish national drug regulatory authority. Norplant consists of six silicone capsules and releases levonorgestrel for five years. Since then several more implants have been registered, and others are under development. Contraceptive implants are now approved in more than 60 countries and have been used by approximately 11 million women worldwide.[3]

The etonogestrel-releasing contraceptive implant, Implanon, was approved by the Dutch drug registration authorities in 1998. The hormone is packed in a single plastic (ethylene vinyl acetate co-polymer) 'rod'. Once inserted, there is a slow release of etonogestrel which inhibits ovulation and thereby provides contraceptive protection for three years.

To a great extent all implantable contraceptives appear effective, with a satisfactory safety profile. Diverse symptoms such as nausea, breast tenderness, pelvic pain, loss of libido and fatigue have typically led to the discontinuation of implants in less than 0.5% users.[4] However, to the extent that implants need to be inserted by a professional, programmatic and operations-dependent adverse events monitoring may be important with this form of contraception.

Operative Issues:
Implantable contraceptives are provider-dependent in the sense that a certain expertise is needed in inserting (and removing) all implantable contraceptive systems. After the procedure, proper insertion has to be ascertained with appropriate techniques. For example, an Implanon 'rod' is placed just under the skin using a special hypodermic injection needle. Providers thus need to be trained in the process. According to the manufacturer's guidance, proper insertion can be ascertained through ultrasound or MRI of the injection site; measuring etonogestrel blood concentration is another option.

Pregnancy and Ectopic Pregnancy:
Needless to say, there is a great risk of pregnancy if the 'rod' (or any other contraceptive system under consideration) is not inserted properly. Further, since progestogen-only contraceptive preparations (POPs) rely mainly on the effects on the cervical mucus and the endometrium for contraceptive efficacy, unintended pregnancies are more likely to be ectopic, possibly due to the reduced activity of the fallopian tube, with additional risks.

WHO data:
From 2001 to date, 289 unintended pregnancies in etonogestrel-implant users were reported to the WHO global database for adverse drug reactions. Of these, 121 reports came from the United Kingdom, 69 from Germany, 53 from the Netherlands, 11 from Switzerland, 10 from Ireland, 7 from Sweden, 6 from Belgium, 6 from Denmark, and 2 each from Australia, Austria and Finland. To date there are 20 reports of ectopic pregnancy in women bearing etonogestrel implants and 13 of these were detailed in a WHO document (Signal 2004-04, prepared by the WHO Collaborating Centre for International Drug Monitoring, Uppsala, Sweden, for restricted distribution). However, it is likely that the manufacturer of the implants has more reports than are available in the WHO database (see section under 'Information from the Swedish Medical Products Agency').

French analysis:
A recent study in France analysed spontaneous reports of unintended pregnancies associated with etonogestrel contraceptive implant use.[5] All cases of unintended pregnancies and all cases of insertion/localization/removal-related events reported to the French Regional Drug Pharmacovigilance Centres and/or to Organon SA (manufacturer of the etonogestrel implant, Implanon) between May 2001 and September 2002 were

analysed. During this period, 108 709 implants had been sold and 39 unintended pregnancies were reported. According to the authors, these pregnancies were mostly due to improper insertions. They concluded that most of the unintended pregnancies could have been prevented by strict adherence to the product instructions, including the fact that the physician who performs the insertion has to be trained in the technique.

Information from the Swedish Medical Products Agency:

Recently, the issues around Implanon-insertion difficulties and reports of pregnancies in women using these implants were discussed in the Swedish Press. Implanon was approved in Sweden in 1999, shortly after the Dutch market approval. Since 2004, Swedish-midwives have had the authority to prescribe, insert and remove Implanon. According to the Swedish Medical Products Agency (MPA), up until August 2004 Organon had received information about 31 pregnancies occurring in connection with Implanon use in Sweden; on the other hand, up until January 2005, the MPA had received spontaneous reports for only six pregnancies in connection with Implanon, which corresponds to 20% of those reported to the manufacturer.[(6)]

According to MPA, of the 31 Swedish-pregnancy reports with Organon, 17 occurred in women in whom the implant was not in place, as determined either by low blood levels of etonogestrel (14 women), ultrasound or MRI (three women); in the remaining 14 cases, five were already pregnant (confirmed) and two were most likely pregnant at the time of injection. In six others there was insufficient information to determine the timing of the observed pregnancies, while in one case the observed pregnancy was most likely due to an interaction between Implanon and an anti-epileptic drug. The MPA is of the opinion that Implanon provides good prevention against pregnancy. It advises that ongoing education and training of providers are important in countering mal-insertions and that physicians and midwives should avail themselves of these educational sessions with practical training prior to inserting Implanon in women. The MPA also reminds providers that all pregnancies due to ineffective hormonal contraceptives should be regarded as serious adverse reactions and reported to the MPA. In addition, difficulties in insertion or removal should also be reported.

Conclusion:

Existing implants are effective and generally safe, provided the quality of services fulfils appropriate standards. In the absence of proper insertion, (ectopic) pregnancy is a clear and present risk with implants. While training providers can promote quality of implant services, monitoring for post-implant pregnancy will help determine the capacity and readiness of the health delivery system in providing the service. It is important to recognize that pregnancy due to an ineffective hormonal contraceptive is a 'serious adverse reaction' and must therefore be reported to the appropriate pharmacovigilance centre.

References:

1. *Population Division (Department of Economic and Social Affairs, United Nations), 2004. 'World contraceptive use in 2003 (Wallchart, available online at www.un.org/esa/population/publications/contraceptive2003/WCU2003.htm).*
2. *Croxatto HB, Diaz S, et al., 1969. Fertility control in women with a progestogen released in micro quantities from subcutaneous capsules. American Journal of Obstetrics and Gynaecology, 105:1135-1138.*
3. *Bongaarts J, Johansson E, 2000. Future trends in contraception in the developing world: prevalence and method mix. Policy Research Division Working Papers No. 141, Population Council, New York, NY. Available at http://www.popcouncil.org/pdfs/wp/141.pdf*
4. *Brache V, Faundes A, et al., 2002. Non-menstrual adverse events during use of implantable contraceptives for women: data from clinical trials. Contraception, 65: 63-74.*
5. *Bensoudaa L, Jonville-Beraa AP et al., 2004. Results of a French Pharmacovigilance survey on the etonogestrel contraceptive implant. (Abstracts of the 8th Annual Meeting of the Société Française de Pharmacologie, Strasbourg, 26-28 April 2004), Fundamental & Clinical Pharmacology 18: 215-268.*
6. *Medical Products Agency (Sweden), 17 January 2005. Information about Implanon. Available at http://www.mpa.se/*

An overview of visual side effects associated with erectile dysfunction agents

Frederick W. Fraunfelder, M.D., Casey Eye Institute, Oregon Health Sciences University, Portland, Oregon

Sildenafil (Viagra®), vardenafil (Levitra®), and longer acting tadalafil (Cialis®) are selective inhibitors of cyclic guanosine monophosphate (cGMP) specific phosphodiesterase type 5 (PDE 5). Sildenafil has up to a 10% inhibitor effect on retinal PDE 6.[1] Tadalafil is more specific to PDE 5 and consequently may produce fewer visual side-effects. The purpose of this review is to convey what is known about the ocular side-effects due to this class of medication.

From 892 case reports of ocular side effects from the WHO spontaneous reporting database, it is evident that all three drugs in this class may cause fully reversible and transitory visual side effects (Table 1). Ocular side-effects are categorized based on the WHO Causality Assessment Guide, which classifies adverse drug reactions (ADR) based on de-challenge and re-challenge with a drug, dosage, time to onset of ADR, and whether there are other explanations for an ADR.[2]

The role of these agents in ischaemic optic neuropathy (ION) is controversial. While up to 20 cases of ION have been reported associated with sildenafil (six in the literature), causation is currently classified as "possible". These agents are weak blood pressure lowering agents, and much stronger blood pressure lowering agents are rarely associated with ION.[3] In addition, a plausible time relationship between drug administration and ION does not exist. Since millions have taken these medications in the age group who get ION, this may be an expected coincidence.

Table 1. Ocular side effects associated with sildenafil, vardenafil and tadalafil

CERTAIN	POSSIBLE (May not be a drug effect)
Changes in colour perception Objects have coloured tinges (usually blue or blue-green, may be pink or yellow) Decreased colour vision Dark colours appear darker	**Mydriasis** (Emotional effect?)
Blurred vision Central haze Transitory decreased vision	**Retinal vascular accidents** (Secondary to exertion?)
Changes in light perception Increased perception of brightness Flashing lights, especially when blinking	**Subconjunctival haemorrhage** (Secondary to exertion?)
ERG changes (transient)	**Ischaemic optic neuropathy**
Conjunctival hyperaemia	
Ocular pain	
Photophobia	

There are 82 case reports from the WHO database of blindness related to sildenafil use. While this ocular event cannot be ruled out, this reviewer suspects that vascular events such as non-arteritic anterior ischaemic optic neuropathy, central retinal artery occlusion, or arteritic ischaemic optic neuropathy could be contributing to these reports as the patients taking sildenafil are the same ones at risk for ocular vascular events. The majority of reports are related to sildenafil as this is the number one seller in the United States and the one drug in this class from which most data will be available.

Sildenafil can be used safely in patients with glaucoma and macular degeneration.[4,5] Post-marketing surveillance of sildenafil, vardenafil and tadalafil has produced no data to date which suggest visual effects due directly to these agents is more than benign and temporary.

References:

1. Marmor FF, Kessler R. *Sildenafil (Viagra) and ophthalmology. Survey of Ophthalmology 1999;44:153-162.*
2. *Edwards R, Biriell C. Harmonisation in pharmacovigilance. Drug Safety 1994; 10:93-102.*
3. *Fraunfelder FT, Fraunfelder FW. Drug-Induced Ocular Side Effects. 5th ed. Woburn, Mass: Butterworth-Heinemann, 2001:824.*
4. *Grunwald JE, Jacob SS, Siu K, Piltz J, Dupont J. Acute effects of sildenafil citrate (Viagra) on intraocular pressure in open-angle glaucoma. American Journal of Ophthalmology 2001;132:872-874.*
5. *Birch DG, Toler SM, Swanson WH, Fish GE, Laties AM. A double-blind placebo-controlled evaluation of the acute effects of sildenafil citrate (Viagra) on visual function in subjects with early-stage age-related macular degeneration. American Journal of Ophthalmology 2002;133:665-672.*

WHO and its drug Prequalification Project: an overview

This little known part of WHO is effective and has teeth that can bite rapidly[1]

Established in 2001, the UN Prequalification Project is an action plan for expanding access to medicines for the hardest hit by HIV/AIDS, Tuberculosis and Malaria while ensuring front-line quality assurance in every step of the medicines supply chain.

The prequalification team within the Department of Medicines Policy and Standards in WHO handles those aspects of the project that ensure safe and efficacious drugs of good quality. The team prepares a list of prequalified medicines that meet certain pre-determined criteria. Drug procurement agencies can then refer to such a list while placing their orders.

Working with a small, quiet and committed group the prequalification team has been successfully addressing the problems of substandard and counterfeit medicines that waste resource, lead to treatment failure, and greatly erode patient confidence and goodwill. With this article, we bring to our readers the reasons for and the remit of the prequalification project and how it operates.

The challenges

The triple menace: HIV/AIDS, tuberculosis (TB) and malaria

Annually, more than six million people die of HIV/AIDS, TB and malaria, compounding the effects of poverty and social inequities in many developing countries. HIV/AIDS has destroyed communities, health-care systems and put a shadow upon the future of entire countries. In poor countries, six million people with HIV/AIDS need immediate antiretroviral therapy. Less than eight per cent get it.[2]

There is a clear need for programmes to improve access to medicines in these sectors. But, for improved access to bear real benefits, all these programmes have to ensure access to medicines of sound quality, safety and efficacy.

Accelerated access and quality assurance

Efforts to accelerate access to pharmaceutical products used in the treatment of these major impact diseases through negotiation and generic competition, have highlighted the importance of building quality assurance into procurement systems for pharmaceutical products and diagnostics. Currently, about 20% of countries have well developed and operational medicines regulation[3]; the rest have either no or limited capacity to adequately regulate the safety, efficacy and quality of medicines circulating in their markets.

In the absence of a quality assurance system, public health agencies risk sourcing substandard, counterfeit and contaminated pharmaceutical products leading to product recalls, waste of resource and mone, with added health risks to patients. While strengthening regulatory systems remains WHO's priority and will continue as part of ongoing health-care initiatives, there is an immediate need to address current gaps in the quality and supply of medicines for major impact diseases.

Treatment failure and risk of resistance

Substandard medicines could result in treatment failure and resistance while exposing patients to the potential risks of chemical impurities. The high failure rate in quality control tests for the antimalarial chloroquine tablets in some sub-Saharan African countries in a recent WHO study highlights this. Only 58% of the medicines tested had an acceptable level of chloroquine content and only 25% had acceptable dissolution properties. The study authors have suggested that poor quality chloroquine may be among the causes of the high rate of resistance in these countries.[4]

Treating patients with poor quality medicines may result in low content of active ingredient and/or low bioavailability leading to drug under-dosage, thus potentially promoting the development of resistance. A system needs to be in place to ensure good manufacturing and clinical practices.

Good Manufacturing Practices (GMP): lack of compliance

In some countries, illegal manufacturing, distribution (including uncontrolled sales in market places and on streets) and smuggling of medicines are widespread. Even manufacturers who fail to comply with good

manufacturing practice (GMP) requirements can still produce medicines for domestic use and for export, no doubt greatly undermining the quality of medicines circulating in the market.

Issues of bioequivalence
Increased availability of medicines can translate into improved access only if these medicines are affordably priced. Quite often, competitive prices are realized through multi-sourcing of products. In those instances where multi-source, generic products are being introduced, it is important to ensure that these generic products are interchangeable with the innovator products in being pharmaceutically and therapeutically equivalent.

An impartial process, that critically evaluates all generic product 'claims' for meeting quality specifications and inspects the manufacturing facility, can ensure that multi-source products are of good quality and therapeutically equivalent to the innovator products.

In short, the WHO commitment to scaling up access to medicines for major-impact diseases is of little relevance to public health if quality, safety and efficacy issues are ignored. The UN Prequalification Project was thus born for ensuring quality, efficacy and safety of priority medicines.

Organization of the overall Prequalification Project
The project is organized and managed by WHO on behalf of the United Nations; UNICEF, UNFPA, UNAIDS are key UN partners with the support of the World Bank. WHO provides the technical and scientific support for quality assurance of medicines and works in close cooperation with qualified assessors and inspectors from national drug regulatory authorities as well as national quality control laboratories of developed countries (e.g., Australia, Canada, EU Member States, Switzerland). Qualified experts from other countries also contribute (e.g., Brazil, Indonesia, South Africa, Uganda, United Republic of Tanzania).

Objectives of the WHO prequalification exercise
The WHO prequalification process aims to:

1. Propose a list of prequalified products as manufactured in sites that meet WHO norms and standards.
2. Follow-up products and manufacturing facilities for quality issues.
3. Ensure that requalification and update of the original approved list is carried out periodically and that variations and changes are correctly controlled.
4. Help national drug regulatory authorities to build capacity in assessment, inspection and control of medicines for priority diseases.

Applying for prequalification
Products identified as being of public health significance are listed on the Prequalification Project web site under "Invitations for Expression of Interest (EOIs: http://mednet3.who.int/prequal).[5] These products are generally selected from the WHO Model List of Essential Medicines. Any manufacturer or supplier of such a product is eligible for assessment in the Prequalification Project by applying (with product dossier etc.) in conformity with WHO guidelines.

The process of prequalification
A team of WHO appointed assessors drawn from national competent authorities will assess the product data as submitted in the dossiers by the interested manufacturers. Additionally, samples may also be analysed for quality control and compared with specifications as provided in the dossier. The manufacturing site(s) and the clinical site (see bioequivalence studies below) listed in the product dossier are inspected on all aspects of Good Manufacturing Practices (GMP) and Good Clinical/Laboratory Practices (GCP/GLP), respectively, by a team appointed by WHO. Normally GMP inspections take a minimum of three consecutive days. In all, the entire process, from receipt of the dossier to prequalification of the product takes about two to four months provided the product dossier is complete at the time of submission and the mentioned sites are up to standards when inspections are due. Frequently however, additional data are requested by the assessors and/or the mentioned sites need to be upgraded to meet requirements. In such cases the time for prequalification of a product may be considerably longer.

Requalification
Manufacturers are required to apply for requalification of their products three years following prequalification. Requalification involves reassessment of the product data as provided in the original product dossier and re-inspection of the relevant site(s) for continued compliance.

Bioequivalence studies
In case of multisource (generic) products, therapeutic equivalence is mostly demonstrated through a bioequivalence study carried out by an independent organization, company, academic institution, research organization or laboratory. Where bioequivalence studies are conducted through contract research organizations (CROs), the CRO study also needs to be inspected as per WHO guidelines.

Outcomes
The immediate outcomes of the WHO prequalification process include the list of prequalified products for treating priority diseases, harmonization of quality requirements for international procurement organizations and strengthening of collaboration between WHO, other UN agencies, related organizations and drug regulatory authorities.

Earlier last year the prequalification process came under some criticism when several antiretroviral drugs were 'de-listed' due to non-compliance with good clinical and laboratory practices (see the prequalification web site for the findings at these inspections, including an additional draft guidance for Contract Research Organizations conducting bioequivalence studies).[5] Two of the products have since been put back on the list after the manufacturer carried out new bioequivalence studies and demonstrated that these two drugs were bioequivalent to and, therefore, as effective and safe as the originator products. Thus, while the de-listing might affect the number of drugs to choose from in the immediate sense, the process always aims to safeguard the patients' well-being. Equally, it shows that here is an impartial system to enforce quality-driven measures, even when dealing with established manufacturers. It is obvious that the prequalification process exists to ensure that "some of the most important drugs are being made safely available in the parts of the world where they are most needed".[1]

References:

1. *Editorial, The Lancet, Volume 364, Number 9448, 2004.*
2. *The 3 by 5 initiative web site: http://www.who.int/3by5/about/en/*
3. *WHO Policy Perspectives on Medicines: Effective medicines regulation: ensuring safety, efficacy and quality, November 2003, World Health Organization.*
4. *The quality of antimalarials. A study in selected African countries. Geneva, WHO, 2003.*
5. *WHO Prequalification Project web site: http://mednet3.who.int/prequal/*

New Zealand's Trans Tasman Therapeutic Products Agency

The Australia-New Zealand joint Therapeutic Products Agency, the Trans Tasman Therapeutic Products Agency will be in operation by 1 July 2006. The agency will assume the responsibilities of the New Zealand (NZ) Medicines and Devices Safety Authority (Medsafe) and Australia's Therapeutic Goods Administration.

New Zealand Media Release,
10 February 2005. Available on the internet at
www.medsafe.govt.nz

Corrigendum

We regret two oversights in the previous issue:

The population of India is 1.049 billion (and not 1.6 billion, as previously stated).

Dr Kris Weerasuriya is the Regional Adviser in EDM, SEARO (not PSM, SEARO).