EDITORIAL

Pharmacovigilance is becoming an important topic and its scope is widening. Exchange of information among regulators, professionals working in pharmacovigilance centres, industry and communication of this information to consumers and the media are being recognized as some of its essential components. This is highlighted in an article found in this issue on the workshop which took place in Hong Kong immediately prior to the tenth International Conference of Drug Regulatory Authorities. A comprehensive study on adverse drug reactions to metamizole in Sweden has recently been published. We have abstracted this article in the section Drugs of Current Interest. It shows definitively that metamizole does carry a high risk of agranulocytosis in Swedish patients.

The third informal consultation meeting on Harmonizing Safety Monitoring was held in WHO, Geneva in early September. A major topic of discussion this year was the linking of pharmacovigilance with public health programmes including malaria, schistosomiasis and HIV/AIDS and ways in which pharmacovigilance could be integrated into these programmes to promote the safe and rational use of medicines.

A WHO-UMC training course on pharmacovigilance will be held in Canberra, Australia at the beginning of November. It is the first time such a course has been held outside Sweden and we are grateful to the Therapeutic Goods Administration (TGA) in Australia for hosting this. We hope to see a large number of you at this course.
# TABLE OF CONTENTS

## REGULATORY MATTERS

<table>
<thead>
<tr>
<th>Topic</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>ARISTOLOCHIC ACID -- Warnings on more products containing Aristolochic acid</td>
<td>1</td>
</tr>
<tr>
<td>ARTHRIN, OSPORO, POENA AND OTHERS -- Presence of undeclared prescription drugs poses health threat</td>
<td>1</td>
</tr>
<tr>
<td>ASPIRIN -- Restrictions on use in children extended to teenagers</td>
<td>1</td>
</tr>
<tr>
<td>BACLOFEN -- Life threatening sequelae and/or death with abrupt withdrawal of intrathecal injections</td>
<td>1</td>
</tr>
<tr>
<td>BEJAI BOWYANTAN -- Risk of toxicity in children due to presence of Borneol</td>
<td>2</td>
</tr>
<tr>
<td>CELECOXIB -- CLASS findings added to product label</td>
<td>2</td>
</tr>
<tr>
<td>EPOETIN-ALFA -- Important safety update</td>
<td>2</td>
</tr>
<tr>
<td>GLITAZONES -- FDA strengthens labelling for cardiovascular risks</td>
<td>3</td>
</tr>
<tr>
<td>HORMONE REPLACEMENT THERAPY (HRT) -- Product information updated</td>
<td>3</td>
</tr>
<tr>
<td>IRINOTECAN -- Labelling updated</td>
<td>3</td>
</tr>
<tr>
<td>ISOTRETINOIN -- Reports of central nervous system disorders</td>
<td>4</td>
</tr>
<tr>
<td>KAVA-KAVA -- More withdrawals due to hepatotoxic risks</td>
<td>4</td>
</tr>
<tr>
<td>MELOXICAM -- Additional information in package insert</td>
<td>5</td>
</tr>
<tr>
<td>MISOPROSTOL -- Major labelling changes</td>
<td>5</td>
</tr>
<tr>
<td>NIMESULIDE -- Temporary suspension pending further evaluation</td>
<td>5</td>
</tr>
<tr>
<td>OLANZAPINE -- Risk of hyperglycaemia</td>
<td>5</td>
</tr>
<tr>
<td>POOLED PLASMA (HUMAN) SOLVENT DETERGENT TREATED -- Boxed warning to indicate new contraindication</td>
<td>6</td>
</tr>
<tr>
<td>PROP O FOL -- Contraindication section modified</td>
<td>6</td>
</tr>
<tr>
<td>ROFECOXIB -- Reports of gastrointestinal/cardiovascular toxicity; labelling updated</td>
<td>6</td>
</tr>
<tr>
<td>SIROLIMUS -- Correction to drug safety information</td>
<td>7</td>
</tr>
<tr>
<td>SLIM 10 -- Withdrawn due to presence of adulterants</td>
<td>7</td>
</tr>
<tr>
<td>TAMOXIFEN -- Boxed warning added to product label</td>
<td>7</td>
</tr>
<tr>
<td>TETRABAMATE -- Withdrawal due to reports of hepatotoxicity</td>
<td>8</td>
</tr>
<tr>
<td>VALPROATE -- Labelling strengthened</td>
<td>8</td>
</tr>
<tr>
<td>ZONISAMIDE -- Prescribing information updated</td>
<td>9</td>
</tr>
</tbody>
</table>

## SAFETY OF MEDICINES

<table>
<thead>
<tr>
<th>Topic</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>BUPROPION -- Safety update</td>
<td>10</td>
</tr>
<tr>
<td>DICLOFENAC &amp; OTHERS -- ADR update from Singapore</td>
<td>10</td>
</tr>
<tr>
<td>GENTAMICIN EAR DROPS -- Risk of ear toxicity in patients with non-intact eardrums</td>
<td>10</td>
</tr>
<tr>
<td>GRAPEFRUIT JUICE -- Potential for drug interactions</td>
<td>10</td>
</tr>
<tr>
<td>MIFEPRISTONE -- New safety information</td>
<td>11</td>
</tr>
<tr>
<td>MIGLUSTAT -- Temporary withdrawal</td>
<td>11</td>
</tr>
<tr>
<td>PALIZUMAB, QUINUPRISTIN + DALFOPRISTIN -- Similar proprietary names could result in medication errors</td>
<td>11</td>
</tr>
<tr>
<td>PERGOLIDE -- Fibrotic reactions with ergot-derived dopamine receptor agonists</td>
<td>11</td>
</tr>
<tr>
<td>PROCARBAZINE -- Risk of lung cancer in Hodgkin’s patients</td>
<td>12</td>
</tr>
<tr>
<td>SILDENAFIL -- 3 years’ post-marketing experience</td>
<td>12</td>
</tr>
<tr>
<td>TICAR CILL -- Haemorrhagic cystitis in patients with cystic fibrosis</td>
<td>12</td>
</tr>
<tr>
<td>TOPIRAMATE -- Reports of acute myopia</td>
<td>13</td>
</tr>
</tbody>
</table>
DRUGS OF CURRENT INTEREST

CYCLO-OXYGENASE (COX) - 2 INHIBITORS -- A summary of adverse drug reactions for COX-2 inhibitors from Canada, New Zealand and UK ................................................................. 14
METAMIZOLE -- Analysis of Swedish adverse reaction reports ..................................................... 15

FEATURE

Recommendations from the Pre-ICDRA (International Conference of Drug Regulatory Authorities) Workshop on ‘The Impact of Regulation on the Safe Use of Drugs’......................................................................................................................... 17

EVENTS & ANNOUNCEMENTS .................................................................................................18
ARISTOLOCHIC ACID

Warnings on more products containing Aristolochic acid

Canada. Health Canada is advising Canadians not to consume Longdan or Lung Tan Xi Gan products since they may contain herbs with aristolochic acid. Aristolochic acid is considered carcinogenic and has been shown to cause mutations in human cells and end-stage kidney failure. Health Canada is working with the manufacturers, distributors and importers to recall these products in Canada. A customs alert has also been issued, to prevent the importation of these products into Canada. Health Canada first issued a warning on aristolochic acid in November 1999 that this ingredient posed a Class I Health Hazard with a potential to cause serious health effects or death.

Readers are referred to previous issues of the WHO Pharmaceuticals Newsletter (Nos. 2&3, 2001; Issue No. 1, 2002; Issue No. 2, 2002) for earlier reports on safety and regulatory measures on aristolochic acid-containing products in other countries.

Reference:
Health Canada Warnings/Advisories, 16 May 2002.
Available from URL:
http://www.hc-sc.gc.ca

BACLOFEN

Life threatening sequelae and/or death with abrupt withdrawal of intrathecal injections

USA, Canada. Novartis Pharmaceuticals Corporation, manufacturer of baclofen intrathecal injection, indicated in the management of severe spasticity of cerebral and spinal origin, has updated the product prescribing information due to rare reports of life-threatening sequelae or death following abrupt withdrawal of the intrathecal therapy. A boxed warning has been added to indicate that abrupt withdrawal could, regardless of cause, result in sequelae including high fever, altered mental status, exaggerated rebound spasticity and muscle rigidity that, in rare cases, could advance to rhabdomyolysis and, multiple organ-system failure and death. Additional details are included in the ‘Warnings’ subsection entitled ‘Withdrawal’. It is noted that, in the first 9 years of marketing, there have been 27 cases of withdrawal-related events temporally related to abrupt discontinuation of baclofen therapy, including 6 fatalities. In most cases, symptoms of withdrawal, which could occur in any patient, appeared within hours to a few days of discontinuation of intrathecal baclofen. Early symptoms may include the additional 5 reported cases in persons aged ≥12 years, in which there was no evidence of aspirin use. The agency says that all possible cases of Reye's syndrome, regardless of the patient’s age or exposure to aspirin, should be reported to the CSM through the Yellow Card Scheme.

Reports in WHO-file: Reye’s syndrome 26

ARTHRIN, OSPORO, POENA AND OTHERS

Presence of undeclared prescription drugs poses health threat

Canada. Health Canada is warning Canadians not to use seven herbal products, namely, Arthrin, Osoro, Poena, Neutralis, Oa Plus, Ra Spes and Hepastat, manufactured by Botanic Lab in the United States since they contain undeclared prescription drugs that could cause serious adverse effects if taken without medical supervision. The prescription drugs include indomethacin (a non-steroidal anti-inflammatory drug), diethylstilbestrol (a non-steroidal estrogen) and alprazolam (an anti-anxiety drug). Consumers are advised to use only those products with an eight-digit Drug Identification Number (DIN) on the label. The DIN indicates that Health Canada has assessed the product for safety, effectiveness and quality. Those who have been using the affected products should discontinue their use and should consult their health care practitioners. Health Canada is working with importers to recall the remaining affected products from the market.

Reference:
Available from URL:
http://www.hc-sc.gc.ca

ASPIRIN

Restrictions on use in children extended to teenagers

UK. Reports of Reye's syndrome associated with aspirin use in children ≥12 years of age have prompted the UK Medicines Control Agency’s Committee on Safety of Medicines (CSM) to revise the prescribing advice for aspirin. The CSM now advises that aspirin use should be avoided in children aged ≤15 years of age, if feverish. The recommendation that aspirin should not be given to children <12 years of age, unless medically indicated, remains unchanged. Although the incidence of Reye's syndrome has declined markedly since 1986, when the CSM advised against aspirin use in children aged <12 years, sporadic cases continue to be reported. Since 1986, the CSM has received 17 reports of Reye's syndrome associated with aspirin use; 7 cases were in children <12 years of age, and 10 were in persons aged ≥12 years. There were an
return of baseline spasticity, pruritus, hypotension, and paraesthesia, while more advanced symptoms may resemble autonomic dysreflexia, sepsis, malignant hyperthermia or neuroleptic malignant syndrome. Prescribers are advised that rapid diagnosis and treatment are required to prevent life-threatening central nervous system and systemic effects of baclofen withdrawal; the recommended treatment for intrathecal baclofen withdrawal is restoration of intrathecal baclofen at the same dosage received before interruption of therapy.

Reference:

BEJAI BOWYANTAN
Risk of toxicity in children due to presence of Borneol

Canada. Health Canada is warning Canadians not to use Bejai Bowyantan in young children and infants since the product contains borneol synthetnicum, a substance known to be extremely toxic, particularly in children. Bejai Bowyantan is a Chinese medicine used to treat babies with flu, fever, stomach aches, diarrhoea, night crying and inability to sleep. Although no adverse reactions to this product have been reported so far, Health Canada is issuing this advice as a precautionary measure and is in the process of identifying all importers of the product to facilitate its rapid removal from the market. A customs alert will prevent the further importation of the product into Canada.

Reference:
Health Canada Warnings/Advisories, 14 Jun 2002.

Available from URL: http://www.hc-sc.gc.ca

CELECOXIB
CLASS findings added to product label

Canada, USA. Changes to the labelling for celecoxib (Celebrex) have been announced in Canada and the US and are based on the results of the Celecoxib Long-term Arthritis Safety Study (CLASS). Celecoxib is a non-steroidal anti-inflammatory drug (NSAID) approved for use in the acute and chronic treatment of osteoarthritis (OA) and rheumatoid arthritis (RA) in adults. Health Canada is advising Canadians that, in the CLASS results:

- There were no differences in the risk of ulcer complications (gastrointestinal bleeding, perforation and obstruction) among the 3 groups of arthritis patients treated with celecoxib (Celebrex, 400 mg twice daily; 4-fold and 2-fold greater than the daily recommended OA and RA doses respectively), diclofenac and ibuprofen (75 mg twice daily and 800 mg thrice daily, respectively; common therapeutics doses for OA and RA).
- In the indicated doses, the risk of ulcer complications and symptomatic ulcers (ulcers with abdominal pain, dyspepsia, nausea or vomiting) was lower for celecoxib (Celebrex) than for ibuprofen, but not different from diclofenac.
- The risk of ulcer complications in patients taking celecoxib (Celebrex) and low dose aspirin was four times that of patients taking celecoxib (Celebrex) alone.
- The US FDA has advised that the following safety data from CLASS be included into the product label
  - The overall safety of celecoxib used (400 mg twice a day) at twice the highest approved dose for rheumatoid arthritis was similar to commonly used doses of diclofenac and ibuprofen
  - The high doses of celecoxib used (400 mg twice a day) were not associated with an increased rate of serious cardiovascular events compared with diclofenac and ibuprofen
  - Patients receiving celecoxib had fewer clinically relevant reductions in haemoglobin compared with patients receiving diclofenac or ibuprofen
  - Patients receiving both low-dose aspirin and celecoxib had a higher rate of gastrointestinal (GI) events than those receiving celecoxib alone.

The new labelling will also include information regarding the risk of serious GI and renal effects in elderly patients.

Reference:

EPOETIN-ALFA
Important safety update

Canada. Janssen-Ortho Inc, in association with Health Canada has issued a ‘Dear Health Professional’ letter about the addition of a boxed section in the product monograph of epoetin-alfa (Eprex). The addition recommends that epoetin-alfa should be administered by the intravenous (IV) route rather
than the subcutaneous (SC) route in patients with chronic renal failure. This advice is based on the fact that most of the worldwide reports of pure red cell aplasia (PRCA) in patients treated with epoetin-alfa have been associated with SC administration of epoetin-alfa. Furthermore, antibodies to erythropoietin were detected in 63 of the 79 cases of PRCA studied. Since scientific literature suggests that all exogenous proteins have the potential to elicit an immune response, particularly when administered by the SC route, the present advise to adopt the IV route of administration aims to reduce the immune response to epoetin-alfa and thereby reduce the incidence of PRCA. Janssen-Ortho will continue to investigate the multiple aspects contributing to antibody formation and PRCA in patients receiving epoetin-alfa.

Reference:

**GLITAZONES**

**FDA strengthens labelling for cardiovascular risks**

**USA.** The US FDA has issued a safety alert advising healthcare professionals of changes to the labelling for pioglitazone (Actos) and rosiglitazone (Avandia). The changes more clearly define the cardiovascular risks associated with the use of thiazolidinediones as monotherapy and in combination with other anti-diabetic agents, particularly insulin. The summary from the FDA alerts physicians and patients to the possibility of fluid retention when either pioglitazone or rosiglitazone are used alone or in combination with insulin and warns that fluid retention may lead to, or exacerbate, congestive heart failure (CHF). It notes that cases of CHF have been reported in association with both agents, post-marketing. Included in the labelling for each drug is information from clinical trials in which the use of pioglitazone or rosiglitazone in combination with insulin was associated with an increased incidence of CHF compared with insulin therapy alone. The labelling for pioglitazone and rosiglitazone advises that patients receiving either agent should be observed for signs and symptoms of heart failure and that, if any deterioration in cardiac function occurs, the drug should be discontinued. Patients are advised to report possible symptoms of heart failure to their physician immediately. Neither drug is recommended for use in patients with New York Heart Association Class III and IV cardiac status.

Reports in WHO-file:
Pioglitazone; Cardiac failure 171, cardiac failure left 5. Rosiglitazone; Cardiac failure 281, cardiac failure left 19, cardiac failure right 1

Reference:

**HORMONE REPLACEMENT THERAPY (HRT)**

**Product information updated**

**UK.** The UK Medicines Control Agency has issued new product information for hormone replacement therapy (HRT), following a review of the risks of cardiovascular disease and cancer associated with HRT by the agency's Committee on Safety of Medicines. To date, no proven benefit or harm has been shown for the use of HRT with respect to cardiovascular disease. Randomised controlled trials showed slightly increased rates of coronary heart disease in the first 1–2 years of HRT use, with a possible decrease in later years. The agency advises that HRT is not indicated for the prevention of cardiovascular disease. Recent randomised controlled trials have confirmed an increased risk of venous thromboembolism (VTE) in women using HRT, and suggest that the risk may be higher than shown in observational studies. The risk of VTE with HRT is higher in older women and in women with other risk factors for VTE. The summary of product characteristics now states that previous estimates of the increased risk of developing breast cancer associated with HRT are numerically uncertain. In addition, new evidence suggests that the increased risk of breast cancer with HRT applies to both estrogen-only therapy and estrogen combined with a progestogen. The addition of a progestogen is not protective and may increase the risk of developing breast cancer. Recent evidence also suggests that the increased risk of endometrial cancer associated with long-term estrogen-only HRT use, compared with non-use, also applies to combined estrogen/progestogen therapy. However, the addition of a progestogen does appear to reduce the risk. Observational studies suggest that, after 10 years of use, there are about 20 extra cases of endometrial cancer per 1000 women treated with combined HRT compared with approximately 42 extra cases of endometrial cancer with estrogen alone. Combined HRT is recommended for women with residual endometriosis, as unopposed estrogen may stimulate residual foci, even after hysterectomy.

Reference:

**IRINOTECAN**

**Labelling updated**

**USA.** Pharmacia, in conjunction with the US FDA, has issued a 'Dear Healthcare Professional'
letter advising prescribers of recent changes to the prescribing information for irinotecan (Camptosar). Irinotecan is indicated as a component for the first-line treatment of metastatic colorectal cancer in combination with 5-fluorouracil (5-FU) and leucovorin and for the treatment of metastatic colorectal cancer that has recurred or progressed following initial 5-FU based treatment.

The prescribing information has been revised to identify patients at higher risk of severe toxicity, to clarify dose modification guidelines and to augment information about the management of treatment-related toxicities. Principal changes reflect that Warnings and Precautions sections of the package insert now state that:

- patients with diarrhoea should be carefully monitored and treated with fluids and electrolytes if they become dehydrated, or with antibacterials if they develop ileus, fever or severe neutropenia
- subsequent courses of antineoplastic therapy should be delayed in patients who develop diarrhoea after the first cycle of treatment until pre-treatment bowel function has resumed for ≥ 24 hours. If grade 2, 3 or 4 late diarrhoea develops, subsequent doses of irinotecan should be reduced.

The FDA has agreed with its Oncologic Drugs Advisory Committee that both the bolus and infusional regimens of irinotecan plus fluorouracil/ leucovorin remain approved for the first-line treatment of metastatic colorectal cancer and that, the starting dose and cycle schedules of both regimens remain unchanged.

Reference:

---

ISOTRETINOIN
Reports of central nervous system disorders

Norway. Reports of central nervous system disorders associated with isotretinoin (Roaccutan) have been received by the Norwegian Medical Products Agency (MPA) and, changes to the product labelling are to be made accordingly. In Norway, isotretinoin is only available through a special license for compassionate use and requires the prescribing physician to take special responsibility for the patient. Included among the reports of psychiatric adverse events the agency has received are two reports of suicidal thoughts and suicide. Although the relationship between isotretinoin and suicide is unclear, the MPA has requested that the manufacturer of ‘Roaccutan’ informs dermatologists that a positive relationship cannot be excluded. In addition, the MPA states that the prescribing physician must evaluate the mental health of the patient before the agent is used and, monitor the patient for depressive symptoms throughout therapy. It has also requested that a warning regarding psychiatric adverse reactions be included in information given to the patient.

Reports in WHO-file:
Depression 1,389, depression aggravated 89, depression psychotic 35, suicide attempt 509

Reference:

KAVA-KAVA
More withdrawals due to hepatotoxic risks

Australia, Germany, UK. Australia’s Therapeutic Goods Administration (TGA) has initiated a voluntary recall of all complementary medicines containing the herb kava. TGA took this action following the death of a woman in Australia who used a medicine containing kava. Sponsors and retailers have been asked to remove all products containing kava from the market place immediately. Consumers have been advised to safely discard kava-containing products in their possession. In addition, the TGA will undertake further evaluation of the use of kava for any additional regulatory action.

As of 17th June the Federal Institute of Germany withdrew all kava-kava and kavain containing products from the German market due to hepatotoxicity risks and insufficiently proven efficacy of these products. The regulation included homeopathic products with dilutions up to D4. The German regulation applies to all kava-containing pharmaceutical formulations.

Following a provisional opinion from the UK Committee on Safety of Medicines (CSM), the Medicines Control Agency (MCA) is to consult on a proposal to prohibit the sale, supply or importation of unlicensed medicinal products containing kava in the UK. The CSM reviewed the issue of kava-associated liver toxicity in December 2001 following the emergence of safety concerns in Europe. At that time, stocks of kava were voluntarily withdrawn by the herbal sector while the safety concerns were under investigation. To date, the MCA is aware of 68 cases worldwide of suspected kava-associated liver problems, including 6 cases of liver failure which resulted in transplant, and 3 deaths. In the UK, there have been 3 reports of kava-associated liver toxicity. The CSM has advised consumers to stop taking medicinal products containing kava, and to seek medical advice if they feel unwell or have concerns about possible liver problems. The MCA’s consultation will last until 27 September 2002.

Readers are referred to WHO Pharmaceuticals Newsletters No. 1 & No. 2, 2002 for all kava-
MELOXICAM

Additional information in package insert

Sultanate of Oman. The Directorate General of Pharmaceutical Affairs and Drug Control (DGPA&DC) of Oman has approved the addition of the following information in the package insert of meloxicam (Moven) capsules:

Drug Interaction: Meloxicam is not recommended with concomitant aspirin therapy due to the possibility of an increase in gastrointestinal ulceration or other complications.

Side Effects: Concomitant use of meloxicam, 15 mg once daily, and lithium doses ranging from 804 to 1072 mg twice daily are known to result in an increase in the mean pre-dose lithium concentration and the area under the curve by 21% when compared to subjects receiving lithium alone. This results from an inhibition of renal prostaglandin synthesis by meloxicam.

Reference:

MISOPROSTOL

Major labelling changes

USA. Changes to misoprostol (Cytotec) labelling have been posted on the US FDA web site.

- The statement that misoprostol (Cytotec) is contraindicated in pregnant women has been removed from the product label. This change is based on the fact that the drug is frequently used to induce labour and delivery and the fact that it is part of the FDA approved regimen for use with mifepristone to induce abortion in pregnancies of 49 days or less.

- The label clarifies that the contraindication in pregnant women concerns those who are using misoprostol to reduce the risk of non-steroidal anti-inflammatory drug-induced stomach ulcers. This does not contraindicate off-label use of misoprostol.

- A Labour and Delivery section has been added that contains safety information regarding the use of misoprostol in these areas.

- The label provides new information that uterine rupture, an adverse event reported with misoprostol (Cytotec) is associated with risk factors such as later trimester pregnancies, higher doses of the drug, prior Caesarean delivery or uterine surgery and having had five or more previous pregnancies.

Reference:
Summary of labelling changes by FDA, 17 Apr 2002.
Available from URL:
http://www.fda.gov

NIMESULIDE

Temporary suspension pending further evaluation

Spain. The Spanish Committee on Safety of Medicines has recommended the temporary suspension of nimesulide products (Antiloxil, Guaxan). The committee has based its proposal on available data that suggest greater hepatotoxic risks with nimesulide than with other available non-steroidal anti-inflammatory drugs. The reactions seem idiosyncratic, unrelated to dose and therefore, unpredictable. The suspension order will be re-considered when the Committee of Proprietary Medicinal Products of the EMEA concludes its current evaluation of the risks with nimesulide.

Reference:
Available from URL:
http://www.msc.es/agemed/csmh/notas/nimesulida.asp

OLANZAPINE

Risk of hyperglycaemia

UK, Japan. Clinical and blood glucose monitoring is recommended in diabetic patients receiving olanzapine, used in the treatment of schizophrenia, says the UK Medicines Control Agency (MCA). Reports of hyperglycaemia and diabetes mellitus associated with the use of olanzapine (Zyprexa) have been received by the agency, prompting appropriate changes to the product information. The MCA has received 40 reports of hyperglycaemia, diabetes mellitus, or exacerbation of diabetes, in association with olanzapine; 4 of the reports involved ketoacidosis and/or coma, including 1 case with a fatal outcome. While the mechanism of this suspected adverse reaction is still under
investigation, rapid bodyweight gain following the initiation of olanzapine therapy may precede the development of hyperglycaemia or exacerbation of pre-existing diabetes. The product information now recommends appropriate clinical and blood glucose monitoring for diabetic patients, and for patients with risk factors for diabetes, who are treated with olanzapine.

The Pharmaceutical & Food Safety Bureau (PFSB) of the Ministry of Health, Labour & Welfare (MHLW), Japan has ordered the revision of the package insert for olanzapine (Zyprexa), a psychotropic drug used in the treatment of schizophrenia. The new package insert will warn about the risk of serious hyperglycaemia with olanzapine and reflect the following information:

Patients with diabetes or with a history of diabetes are additionally contraindicated to the use of olanzapine; special care is required in patients with risk factors for diabetes, such as family history of diabetes, hyperglycaemia, obesity etc; careful follow-up procedures including glycaemia check should be in-place during olanzapine administration. Medical professionals should brief patients and family members about the risks and symptoms of hyperglycaemia.

The MHLW issued the above order following several reports of hyperglycaemia (nine with two deaths) in which causality with the use of olanzapine could not be ruled out.

The PFSB has also instructed Eli Lilly Japan K.K., the manufacturer of olanzapine (Zyprexa) to distribute a dear-doctor letter for the above information.

Reports in WHO-file:
Diabetes mellitus 163, diabetes mellitus aggravated 24, hyperglycaemia 295

Reference:

POOLED PLASMA (HUMAN) SOLVENT DETERGENT TREATED

Boxed warning to indicate new contraindication

USA, Canada. Health professionals are advised of the addition of a boxed warning in the labelling for pooled plasma, solvent detergent treated (PLAS+SD). The new Boxed Warning contraindicates the use of this product in patients undergoing liver transplant, patients with severe liver disease and known coagulopathies. The Warnings section has also been strengthened to indicate that patients receiving large volumes of this product should be monitored for evidence of thrombosis, excessive bleeding or exacerbation of disseminated intravascular coagulation (DIC).

Reference:

ROFECOXIB

Reports of gastrointestinal/cardiovascular toxicity; labelling updated

Canada, USA. Health Canada is advising consumers of safety information related to the selective cyclo-oxygenase (COX-2) inhibitor rofecoxib (Vioxx), a non-steroidal anti-inflammatory drug (NSAID) approved for the treatment of osteoarthritis, menstrual pain and acute pain in propofol. The revised monograph will include the following statement: ‘Propofol is contraindicated for sedation of children 18 years or younger receiving intensive care’. As of 10 July 2002, there were 6 reports of a constellation of serious adverse events characterized by metabolic acidosis, hemodynamic instability and cardiac conduction abnormalities in children receiving propofol infusions in an ICU setting in Canada. Three of these reports had a fatal outcome.

Readers are referred to an earlier ‘Dear Healthcare Professional’ letter issued by AstraZeneca in consultation with US FDA (WHO Pharmaceuticals Newsletter Nos. 2 & 3, 2001) emphasising that propofol (Diprivan) is not indicated for sedation in paediatric patients. The US FDA had determined that important safety concerns exist for propofol as a sedative in paediatric patients in intensive care.

Reports in WHO-file:
Acidosis 85

Reference:

PROPOFOL

Contraindication section modified

Canada. Following consultation with Health Canada, all licensed providers of propofol are revising the Contraindication and Dosage and Administration sections of the product monograph for propofol. The revised monograph will include the following statement: ‘Propofol is contraindicated for sedation of children 18 years or younger receiving intensive care’. As of 10 July 2002, there were 6 reports of a constellation of serious adverse events characterized by metabolic acidosis, hemodynamic instability and cardiac conduction abnormalities in children receiving propofol infusions in an ICU setting in Canada. Three of these reports had a fatal outcome.

Readers are referred to an earlier ‘Dear Healthcare Professional’ letter issued by AstraZeneca in consultation with US FDA (WHO Pharmaceuticals Newsletter Nos. 2 & 3, 2001) emphasising that propofol (Diprivan) is not indicated for sedation in paediatric patients. The US FDA had determined that important safety concerns exist for propofol as a sedative in paediatric patients in intensive care.

Reports in WHO-file:
Acidosis 85

Reference:

ROFECOXIB

Reports of gastrointestinal/cardiovascular toxicity; labelling updated

Canada, USA. Health Canada is advising consumers of safety information related to the selective cyclo-oxygenase (COX-2) inhibitor rofecoxib (Vioxx), a non-steroidal anti-inflammatory drug (NSAID) approved for the treatment of osteoarthritis, menstrual pain and acute pain in propofol. The revised monograph will include the following statement: ‘Propofol is contraindicated for sedation of children 18 years or younger receiving intensive care’. As of 10 July 2002, there were 6 reports of a constellation of serious adverse events characterized by metabolic acidosis, hemodynamic instability and cardiac conduction abnormalities in children receiving propofol infusions in an ICU setting in Canada. Three of these reports had a fatal outcome.

Readers are referred to an earlier ‘Dear Healthcare Professional’ letter issued by AstraZeneca in consultation with US FDA (WHO Pharmaceuticals Newsletter Nos. 2 & 3, 2001) emphasising that propofol (Diprivan) is not indicated for sedation in paediatric patients. The US FDA had determined that important safety concerns exist for propofol as a sedative in paediatric patients in intensive care.

Reports in WHO-file:
Acidosis 85

Reference:
REGULATORY MATTERS

adults. Results from a post-market clinical trial (VIGOR: Vioxx Gastrointestinal Outcomes Research) show that a risk of gastrointestinal toxicity associated with the use of rofecoxib exists although to a lesser extent than another NSAID, naproxen. Results also show a higher rate of cardiovascular adverse events in the rofecoxib group. Patients experiencing symptoms of gastrointestinal toxicity such as gastric pain and blood in stools and those who develop fluid retention or swelling, shortness of breath, weakness, fatigue, excessive weight gain or chest pain while on rofecoxib therapy should inform their physician immediately. In addition, patients with a medical history of hypertension, ischaemic heart disease, fluid retention or heart failure are advised to discuss their medical condition with their physician before taking rofecoxib.

A ‘Dear Healthcare Professional’ letter issued by Merck regarding changes to the labelling for rofecoxib (Vioxx) has been posted on the US FDA website. The letter advises of updates made to the Warnings, Precautions and Clinical Studies sections of the labelling, and includes new cardiovascular and gastrointestinal safety information, also derived from analyses of the VIGOR study, that rofecoxib was associated with a significantly higher rate of serious cardiovascular thrombotic events and, a significantly lower incidence of serious upper gastrointestinal adverse events, compared with naproxen. The labelling also includes the recommended daily dose of rofecoxib for the treatment of rheumatoid arthritis, a recently approved indication.

References 3 and 4 below provide more information on the VIGOR study.

Reference:

Available from URL:
http://www.hc-sc.gc.ca


SIROLIMUS
Correction to drug safety information

USA, Canada. In April 2002 the US FDA had posted a letter from Wyeth Pharmaceuticals informing clinicians of the risk of hepatic artery thrombosis (HAT), graft loss and death associated with the use of sirolimus (Rapamune) in de novo transplantation. More recently Wyeth-Ayerst Canada Inc, in consultation with Health Canada has issued a letter to health care providers advising them of the following correction to the product monograph for sirolimus (Rapamune). The updated monograph will reflect the following:

- The safety and efficacy of sirolimus (Rapamune) have not been established in liver transplant patients, and therefore, such use is not recommended.

- In a study in de novo liver transplant patients, the use of sirolimus in combination with tacrolimus was associated with excess mortality and graft loss, many of whom had evidence of infection at or near the time of death.

- In addition, the use of sirolimus in combination with ciclosporine or tacrolimus was associated with an increase in HAT; most cases of HAT occurred within 30 days of post-transplantation and most led to graft loss or death.

Reference:


SLIM 10
Withdrawn due to presence of adulterants

Singapore. The Singapore health authority has ordered the withdrawal of Slim 10, a herbal product of Chinese origin, popular as a slimming pill. This measure follows more than 20 reports of hyperthyroidism and 2 reports of fulminant hepatic failure in consumers using the product in Singapore. Slim 10 was originally declared to contain only 5 herbal ingredients, namely herba gynostemmae pentaphylli, folium gemmae camelliae sinensi, succus aloes folii siccatus, semen raphani and fructus crataei. However, the Singapore Pharmacovigilance Centre has detected the presence of adulterants fenfluramine and thyroid gland components in Slim 10. The centre is in the process of investigating the causal relationship of Slim 10 to liver toxicities.

Reference:
Communication from Head (Pharmacovigilance), Centre for Pharmaceutical Administration, Health Sciences Authority, Singapore, 19 Jul 2002.

TAMOXIFEN
Boxed warning added to product label

USA. The labelling of AstraZeneca’s tamoxifen (Nolvadex) has been revised to include a boxed warning highlighting the increased risk of uterine malignancies, stroke and pulmonary embolism, and the Warnings section has been

Available from URL:
http://www.fda.gov/ohrms/dockets

WHO Pharmaceuticals Newsletter No. 3, 2002 • 7
extended. AstraZeneca has issued a ‘Dear Doctor’ letter advising that the prescribing information now includes a new boxed warning. The warning contains new information of particular relevance to women with ductal carcinoma in situ (DCIS) and women at high risk for developing breast cancer who are receiving or considering tamoxifen therapy to reduce their risk of developing invasive breast cancer. It states that serious and life-threatening events associated with tamoxifen in this risk reduction setting include uterine malignancies, stroke and pulmonary embolism, some of which may be fatal. Estimated incidence rates for the events are also presented. The Warnings section advises that, while most uterine malignancies seen in association with tamoxifen are adenocarcinomas of the endometrium, uterine sarcoma, the diagnosis of which is generally associated with a poorer prognosis and shorter survival time, has been reported to occur more frequently in long-term tamoxifen users than in non-users; some of these malignancies have been fatal. Patients with prior or present exposure to tamoxifen should be advised to undergo annual gynaecological examinations and to report any gynaecological abnormalities to their physician immediately. Healthcare providers are advised to discuss the potential benefits and risks of tamoxifen therapy with patients, particularly women with DCIS and those at high risk for developing breast cancer who are considering taking tamoxifen to reduce their risk. However, it is also stated that in women already diagnosed with breast cancer, the benefits of tamoxifen therapy far outweigh the risks.

**Reference:**
Available from URL:
http://www.fda.gov/medwatch/SAFETY/2002/may02.htm

---

**TETRABAMATE**

**Withdrawal due to reports of hepatotoxicity**

**Spain.** The Spanish Committee on the Safety of Medicines has re-evaluated the risk-benefit of tetrabamate (complex of phenobarbital, difebarbamat and febarbamat) and recommended its suspension from the Spanish market. Tetrabamate appears to be strongly hepatotoxic and offers no advantage over other treatments for alcoholic withdrawal syndrome such as the benzodiazepines.

**Reference:**
Available from URL:
http://www.msc.es/agemed/csmh/

---

**VALPROATE**

**Labelling strengthened**

**USA.** Abbott Laboratories and the US FDA have strengthened the Contraindications, Warnings and Precautions sections of the product labels for the anticonvulsants valproate semisodium (divalproex sodium) and valproic acid, following reports of valproate-induced hyperammonaemic encephalopathy, including fatalities, in patients with urea cycle disorders (UCDs). The company has issued a ‘Dear Healthcare Professional’ letter advising prescribers of the labelling revisions that have been made to all Abbott Laboratories valproate products (Depakote Tablets, Depakote ER Tablets, Depakote Sprinkle Capsules, Depakene capsules and syrup, and Depacon for injection). It is noted that UCDs are a group of uncommon genetic abnormalities estimated to occur in between 1:8000 and 1:30 000 births. Patients with UCD have an impaired ability to produce urea (an end-product of ammonia metabolism), due to a defect or deficiency in one of the enzymes of the urea cycle. The product labelling now states that valproate semisodium and valproic acid are contraindicated in patients with known urea cycle disorders. The ‘Warnings’ sections now state that evaluation for UCD should be considered in the following patients:

- those with a history of unexplained encephalopathy, coma, or mental retardation, and those with a protein load, pregnancy-related or postpartum encephalopathy, or a history of elevated plasma ammonia or glutamine
- those with a history of cyclical vomiting and lethargy, episodic extreme irritability, ataxia, low blood urea nitrogen, or protein avoidance
- those with a family history of UCD or unexplained infant mortality (particularly males)
- those with other signs or symptoms of UCD.

The Precautions section states that patients who develop unexplained lethargy and vomiting or changes in mental status while receiving valproate semisodium or valproic acid should be evaluated for hyperammonemnic encephalopathy and their plasma ammonia level measured. If the ammonia level is increased, valproate therapy should be discontinued and appropriate interventions initiated. Such patients should undergo investigation for underlying UCD. Revisions consistent with those made to the product labels have also been made to the ‘Information for Patients’ subsection of the Precautions’ and Adverse Reactions sections of the label.

**Reports in WHO-file:**
Encephalopathy 254

**Reference:**
Available from URL:
http://www.fda.gov/medwatch/Safety/2002/safety02.htm#depako
ZONISAMIDE
Prescribing information updated

USA. Elan Pharmaceuticals has issued a 'Dear Healthcare Professional' letter in the US advising prescribers of important updates to the prescribing information for zonisamide (Zonegran) used in the treatment of refractory epilepsy. The update provides new information about oligohidrosis and hyperthermia in paediatric patients. The company says that, as of December 2001, there have been 40 reported cases of oligohidrosis and hyperthermia in paediatric patients. 38 cases were reported during the first 11 years of marketing in Japan and 2 cases were reported in the first year of marketing in the US, providing estimated reporting rates of 1 and 12 cases per 10,000 patient-years of exposure, respectively. The cases typically involved decreased sweating and elevated body temperatures and many were reported after exposure to elevated environmental temperatures. Some patients developed heat stroke requiring hospitalisation, but no deaths have been reported.

The company says that paediatric patients appear to be at an increased risk of zonisamide-associated oligohidrosis and hyperthermia. Patients, particularly paediatric patients receiving zonisamide should be monitored for evidence of decreased sweating and elevated body temperature, particularly in warmer weather. Prescribers are also advised to use caution when prescribing zonisamide with other drugs that may predispose patients to heat-related disorders such as carbonic anhydrase inhibitors or drugs with anticholinergic activity.

Elan Pharmaceuticals also notes that the safety and efficacy of zonisamide in paediatric patients has not been established and that zonisamide is not approved for use in paediatric patients.

Reference:

Reports in WHO-file: Sweating decreased 13
BUPROPION

Safety update

UK. Further to the Media Release
on the risk of seizures with
bupropion (Zyban) as an aid to
smoking cessation (WHO
Pharmaceuticals Newsletter No. 2,
2002), the UK Medicines
Control Agency (MCA) has issued
a new safety update for the drug
that includes a reminder to
prescribers that bupropion is
contraindicated for use in
patients with previous or current
seizure disorders. Up to 8 April
2002, the MCA had received
a total of 7472 reports of
suspected adverse reactions
associated with bupropion
(Zyban) via the Yellow Card
Scheme. However, it is
emphasised that these suspected
reactions may be associated with
other factors, such as nicotine
withdrawal, or concomitant
medicines or illnesses. The most
commonly reported reactions
included insomnia (979 reports),
urticaria (973), rash (962),
headache (765), dizziness (732),
nausea (629), depression (462),
pruritus (373), tremor (346),
cheast pain (345), anxiety (306),
abdominal pain (241),
palpitations (238), dry mouth
(238), vomiting (230), dyspnoea
(229), agitation (201), increased
sweating (195), arthralgia (179),
chest tightness (177) and
seizures (176). In approximately
one-half of the 176 reports of
seizures, patients had either a
history of seizures or risk factors
for them. Of the 7472 reports
received to date, 58 had a fatal
outcome. However, in the
majority of these, the underlying
condition of the patient may
provide an alternative
explanation; cardiovascular
disorders were the reported cause of death in 80% of them. In 14 cases with
a fatal outcome, patients were
not receiving bupropion (Zyban)
at the time of death. It is estimated
that, up to 21 December 2001, 513 000
patients in the UK had received
bupropion (Zyban).

Reference:
Medicines Control Agency. Zyban
(bupropion hydrochloride) - safety
update, Internet Document, 19 Apr
2002.
Available from URL:
http://www.mca.gov.uk

DICLOFENAC &
OTHERS

ADR update from
Singapore

The Pharmacovigilance Unit of
the Health Sciences Authority in
Singapore received a ‘record
number’ of adverse event reports
in 2001; 561 reports were
received by the agency, 24% of
which were serious. There were
9 fatal cases in which the
outcome was thought to be
directly caused, or, precipitated
by the suspected drug. Adverse
events resulted in hospitalisation
in 27% of patients, and a further
23% were already hospitalised at
the time of the event. The
majority (73.6%) of the reports
were received from public sector
hospitals, followed by private
hospitals (14.4%) and general
practitioners (6.4%). The most
commonly reported events were
rash (184 reports), periorbital
oedema (142), urticaria (116),
abnormal blood counts (28),
acute respiratory distress (25)
and liver disorders (22).
Diclofenac, naproxen, ibuprofen,
ceftazidime, cefmenac, acid,
cotrimoxazole (trimethoprim/
sulfamethoxazole) and rofecoxib
were the drugs most often
associated with adverse events.

Reference:
Adverse Drug Reaction News
(Singapore) 4: 2-3, Mar 2002.

GENTAMICIN
EAR DROPS

Risk of ear toxicity in
patients with non-
intact eardrums

Canada. Schering Canada Inc, in
consultation with Health Canada
has advised health care
professionals on the risk of
ototoxicity with the use of topical
gentamicin sulfate (Garasone
and Garamycin) ear drops in
patients with perforated
tympanic membranes. This
advice is based on post-
marketing reports of rare cases
of ototoxicity (hearing loss,
tinnitus, vertigo, ataxia or
oscillopia) following the use of
otic gentamicin in the presence
of tympanic membrane
perforation. Health Professionals
are required to monitor the
patients regularly and reassess
the need for therapy, with
respect to ototoxicity, 5-7 days
after start of treatment. A Health
Canada Advisory has also been
issued to convey the above
information to the general public.

Reference:
1. ‘Dear Healthcare Professional’
letter by Schering Canada Inc,
30 May 2002.
Available from URL:
http://www.hc-sc.gc.ca
2. Health Canada
Warnings/Advisories,
4 Jun 2002.
Available from URL:
http://www.hc-sc.gc.ca

GRAPEFRUIT
JUICE

Potential for drug
interactions

Canada. Health Canada is
advising the public not to take
grapefruit or its juice (fresh or
frozen) with certain drugs since
several substances in grapefruit
may interfere with their
metabolism, leading to higher
blood levels of these drugs with
serious and even life-threatening
adverse reactions. Affected
products include (but not limited
to) drugs used in treating
medical conditions such as angina, anxiety, cancer, convulsions, depression, erectile dysfunction, gastrointestinal reflux, high blood pressure, high lipid cholesterol levels, HIV/AIDS, infections, irregular heart rhythms, organ graft rejections and psychotic problems. As little as one glass of grapefruit juice can cause an increased blood drug level and the effects can last for three days or more. Health Canada has issued several communication documents to remind health professionals of possible interactions between grapefruit and drugs. In addition, Health Canada is working with drug manufacturers whose products are adversely affected by grapefruit, to ensure that the relevant information is placed on the product label.

Reference:

MIFEPRISTONE
New safety information

USA. Danco Laboratories, in association with the US FDA, has issued a 'Dear Healthcare Provider' letter containing new safety information for mifepristone (Mifeprex). The letter states that a small number of reports of ruptured ectopic pregnancies have been received, including one report of haemorrhage that had a fatal outcome. Prescribers are reminded that ectopic pregnancy is a contraindication for use of mifepristone and they should be aware of the possibility of ectopic pregnancy throughout the mifepristone treatment period. The company also states that 2 cases of serious systemic bacterial infection, one of which had a fatal outcome, have been reported following treatment with mifepristone plus misoprostol. It is noted that abortion, childbirth and menstruation can result in infection; these drugs are not considered to be associated with any special risk of infection. A report of myocardial infarction that occurred in a 21-year-old woman, 3 days after use of mifepristone plus misoprostol, has also been received. The letter states that no causal relationship has been established between any of the events listed and the use of misoprostol.

Reference:

MIGLUSTAT
Temporary withdrawal

Israel. Oxford GlycoSciences has temporarily halted miglustat (OGT 918, ’Vevesca’, used in the treatment of Type I Gaucher disease) usage in Israel as a precaution pending investigation of an unexplained adverse event in a patient previously treated with the drug. The company has been notified that a 66-year old patient, who received miglustat in a clinical trial and then, through the extended-use capture protocol until stopping treatment in October 2001, has developed cognitive dysfunction. The company states that the patient is undergoing investigations and that there are other potential causative factors relevant to the event. Until the results of these investigations become available, the Ethics Committee in Israel has recommended that the use of miglustat be temporarily withdrawn.

Reference:

PALIZUMAB, QUINUPRISTIN + DALFOPRISTIN
Similar proprietary names could result in medication errors

Japan. The Drug and Food Safety Bureau in Japan has asked Aventis Pharma and Dainabot to take appropriate measures to prevent possible medication errors with their new products of quinupristin-dalfopristin (Aventis’ Synercid) and palizumab (Dainabot’s Synagis). The former (quinupristin-dalfopristin) is used in the treatment of vancomycin-resistant Enterococcus infections and the latter (50 and 100 mg IM injections of palizumab) is an antiviral agent. The safety division has pointed out that medication errors could occur due to the products having similar proprietary names. The two companies have assured to take appropriate preventive measures.

Reference:
Pharma Japan 1793, p. 17, 29 Apr & 6 May 2002.

PERGOLIDE
Fibrotic reactions with ergot-derived dopamine receptor agonists

UK. The UK Medicines Control Agency reports that pergolide appears to be associated with a higher reporting rate of fibrotic adverse reactions in the UK than other ergot-derived dopamine receptor agonists. In total, 49 suspected fibrotic reactions associated with pergolide (Celance) have been reported in the UK through the Yellow Card reporting scheme, compared with 24 fibrotic reactions reported in association with bromocriptine (Parlodel) and 6 with cabergoline (Cabaser). There have been no reported fibrotic reactions associated with lisuride. The total numbers of all
adverse reactions reported in association with pergolide, bromocriptine, cabergoline and lisuride were 496, 942, 367 and 73, respectively. Suspected fibrotic reactions reported included pulmonary and pleural fibrosis, pleural effusion, retroperitoneal fibrosis and constrictive pericarditis. The agency notes that many of the reported cases of fibrosis were discovered at an advanced stage, and 3 patients died. It suggests that the performance of baseline laboratory tests and chest x-rays prior to starting treatment with ergot-derived dopamine receptor agonists may be appropriate and, if long-term therapy is envisaged, lung function tests may also be useful. As fibrotic disorders may have an insidious onset, the agency advises prescribers to be aware of symptoms arising from fibrotic reactions, including unexplained or progressive dyspnoea, pleuritic or pericardial pain, abdominal discomfort or distension, oedema and renal insufficiency, and that patients receiving ergot derivatives should be carefully monitored for these symptoms. The agency adds that progression of fibrotic reactions can be prevented by early diagnosis and withdrawal of ergot derivatives.

Reference:

PROCARBAZINE
Risk of lung cancer in Hodgkin’s patients

Canada. Sigma-tau Pharmaceuticals Inc, Canada, has issued a ‘Dear Healthcare Professional’ letter informing them of new safety information for procarbazine hydrochloride (Matulane), one of the components of MOPP regimen (mechlorethamine, vincristine, procarbazine and prednisone) used in treating Hodgkin’s disease. Literature reports reveal that lung cancer can develop as a secondary non-lymphoid malignancy in Hodgkin’s patients receiving MOPP therapy and radiation, taking into account tobacco use. Results indicate an increased risk of lung cancer in a dose dependent fashion which increases with tobacco use. Patients are advised to cease smoking before starting MOPP therapy.

Reference:

SILDENAFIL
3 years’ post-marketing experience

Australia. Since the introduction of sildenafil (Viagra) to the Australian market more than 3 years ago, the Australian Adverse Drug Reactions Advisory Committee (ADRAC) has received 773 reports of adverse reactions associated with its use; in 741 reports, sildenafil was the sole suspected drug. The most commonly reported reactions were relatively minor in nature and consistent with those observed during clinical trials, including headache (233 reports), flushing (139), abnormal vision (65), rhinitis (42), dizziness (31), dyspepsia (28), nausea (27), abdominal pain, palpitation and priapism (16 reports each). However, ADRAC has also received 20 reports of myocardial infarction (MI) associated with sildenafil (including 4 with fatal outcomes), 26 reports of chest pain, and 10 other reports with a fatal outcome (6 unexplained deaths, 2 strokes and 2 subarachnoid haemorrhages). The committee notes that the ingestion of sildenafil was temporally associated with only 23 of these 56 adverse events. Furthermore, of the 20 cases of myocardial infarction, 9 had or were at high risk of cardiovascular disease and 1 was receiving concomitant nitrates.

The committee says that the contribution of sildenafil to cardiac events is difficult to assess, but notes that a recent publication shows no evidence for an increased risk of fatal myocardial infarction or ischaemic disease among sildenafil users. ADRAC reminds prescribers that sildenafil is contraindicated in men with severe cardiovascular disease, heart failure or unstable angina pectoris and, since sildenafil can potentiate the hypotensive effects of nitrates, co-administration with nitrates is also contraindicated.

Reference:

TICARCILLIN
Haemorrhagic cystitis in patients with cystic fibrosis

Australia. Since 1980, the Australian Adverse Drug Reactions Advisory Committee (ADRAC) has received 15 reports of haemorrhagic cystitis associated with the use of ticarcillin alone (no longer available) or ticarcillin/clavulanic acid (Timentin). In all cases, the patients (9 males and 6 females, aged 2−19 years) were receiving ticarcillin for the treatment or prophylaxis of infections complicating cystic fibrosis, and the reaction occurred within 4 hours to 3 weeks of treatment initiation. Three patients experienced a recurrence of the reaction on rechallenge with the drug; 1 patient received 3 courses of treatment with ticarcillin and each time the reaction occurred after a shorter time interval following administration of each course.

From the reports received by ADRAC, paediatric patients with cystic fibrosis appear to be most at risk of developing ticarcillin-associated haemorrhagic cystitis; the committee notes that prompt diagnosis and withdrawal of
ticarcillin usually results in rapid symptom resolution.

Reports in WHO-file:
Cystitis haemorrhagic 9

Reference:

TOPIRAMATE

Reports of acute myopia

UK. The risk of acute myopia and increased intraocular pressure associated with topiramate (Topamax) has been highlighted by the UK Medicines Control Agency. Worldwide, there have been 23 cases of acute myopia with secondary angle-closure glaucoma reported in association with topiramate, involving both children and adults. The symptoms include decreased visual acuity and/or ocular pain and typically occur within the first month of treatment. Examination may reveal bilateral myopia, hyperaemia, a shallow anterior chamber and increased intraocular pressure, with or without mydriasis. Anterior displacement of the lens and iris due to choroidal effusions has also been reported. If raised intraocular pressure occurs, the agency recommends that specialist ophthalmological advice should be sought. Appropriate measures should be taken to reduce intraocular pressure and topiramate should be discontinued; these measures generally result in rapid resolution of the ocular symptoms.

Reports in WHO-file:
Myopia 22

Reference:
DRUGS OF CURRENT INTEREST

CYCLO-
OXYGENASE
(COX) - 2
INHIBITORS
A summary of adverse
drug reactions for COX-
2 inhibitors from
Canada, New Zealand
and UK

Cardiovascular/
cerebrovascular events:
Up to 12 October 2001, Health
Canada had received 70 reports
of suspected cardio-vascular/
cerebrovascular adverse re-
actions in association with
celecoxib and 68 in association
with rofecoxib, marketed in
Canada since April and
November 1999, respectively. Of
these, 7 celecoxib and 9
rofecoxib reports had a fatal
outcome; most of these patients
had presented with multiple
adverse reactions, had pre-
existing medical conditions or
were receiving concomitant
medication. The most commonly
reported events were heart rate
and rhythm disorders, increased
BP, congestive heart failure,
myocardial infarction, cerebro-
vascular events and thrombo-
embolic events. Health Canada
cautions that factors such as
pre-existing medical conditions,
the prevalence of cardiovascular
disease in the drug target
population and concomitant use
of drugs that may cause
cardiovascular adverse reactions
or interactions, must be
considered when interpreting
these data. Of the 7 fatal cases
of cardiovascular reactions
reported in association with
celecoxib, 2 were cases of
cerebral haemorrhage in patients
receiving concomitant warfarin.
Health Canada says that caution
should be exercised when
prescribing COX-2 inhibitors to
patients at risk of cardiovascular
disease and that patients should
be advised to report any
symptoms of cardiovascular
events to their physician
immediately.

Gastrointestinal (GI) toler-
ability overview:
Although COX-2 inhibitors are
associated with a reduced risk of
GI adverse events compared
with conventional NSAIDs, GI
events still account for
approximately 30% of COX-2
inhibitor-related adverse events
reported in New Zealand,
according to Dr Ruth Savage
from the Centre for Adverse
Reactions Monitoring (CARM),
New Zealand. CARM has received
65 reports of GI adverse events
attributed to celecoxib, of which
17 were serious; these included
reports of melena,
gastroduodenal ulcer, intestinal
perforation and 3 deaths. All but
2 patients had ≥1 risk factor for
GI ulceration and 14 patients
were aged ≥ 75 years. GI
adverse events have also been
reported in association with
rofecoxib, although it was noted
that, at the time of analysis, the
use of rofecoxib in New Zealand
was half that of celecoxib. Dr
Savage notes that, while the
results of 2 large studies (the
VIGOR and CLASS trials) showed
a 50% reduction in risk of
gastrointestinal ulcer
complications with COX-2
inhibitors compared with
conventional NSAIDs, the use of
COX-2 inhibitors still confers a 2-
fold increase in risk of gastro-
duodenal ulcer complications
compared with non-use. Reports
received by CARM suggest that
serious GI events occur
predominantly in older patients
and those with other risk factors
but adds that this may be a
reflection of preferential
prescribing of COX-2 inhibitors to
at-risk patients.

Dr Savage says that COX-2
inhibitors should not be
prescribed to patients with active
gastroduodenal disease, and
suggests that the concomitant
use of a gastro-protective agent
should be considered when
prescribing COX-2 inhibitors to
patients with a history of serious
GI reactions to conventional
NSAIDs. She also suggests that
both conventional NSAIDs and
COX-2 inhibitors should be
prescribed at the lowest effective
dose and preferably be restricted
to short-term or intermittent
use. Patients who develop pain,
bleeding, signs of obstruction or
altered bowel habits while using
conventional NSAIDs or COX-2
inhibitors should discontinue
treatment, pending investigation.

The UK Medicines Control
Agency (MCA) has issued
updated advice regarding the
safe use of NSAIDs following a
recent assessment of Yellow
Card data, epidemiological
studies and published literature;
the results are consistent with a
previous risk assessment for 7
non-aspirin NSAIDs issued by
the agency in 1994 (see table).
An analysis of Yellow Card
reports of gastrointestinal (GI)
perforation/obstruction, ulcera-
tion or bleeding with diclofenac,
naproxen and ibuprofen for risk
factors revealed that 71% of
patients were aged > 65 years,
28% were receiving concomitant
aspirin, 6% were receiving
another non-aspirin NSAID and
3% had a history of GI events.
The agency notes that the risk of
GI ulceration or bleeding is more
than doubled when aspirin is
combined with non-aspirin
NSAIDs. Although the results of
clinical trials suggest that the
cyclo-oxygenase (COX)-2 in-
hibitors, rofecoxib and celecoxib,
have a reduced risk of GI
adverse events compared with
non-selective NSAIDs, the MCA
notes that Yellow Card reports of
GI perforation/obstruction,
ulceration or bleeding have been
received in association with
these drugs. Up to September
2001, the reporting rates of
these GI events with rofecoxib
and celecoxib were 8.4 and 9
per 100 000 prescriptions,
respectively.

For the safe use of NSAIDs
the MCA advises that:

- NSAIDs with a low risk of GI
ulceration or bleeding should
be used preferentially.
- NSAIDs should be started at
the lowest recommended
dose.
Most of the reports involved elderly patients and a higher proportion of patients were women. In all cases, the acute psychiatric reaction resolved rapidly upon withdrawal of the COX-2 inhibitor.

Reference:

METAMIZOLE
Analysis of Swedish adverse reaction reports

In one of the earlier issues of the WHO Pharmaceuticals Newsletter (Issue No. 1, 2002) we published a discussion paper entitled ‘A reappraisal of antipyretic and analgesic drugs’ by Dr Anthony Wong, University of Sao Paulo, Brazil. The author discussed the continued presence of metamizole sodium (dipyrone) in the Brazilian market despite reports of metamizole-induced agranulocytosis in other countries. As anticipated, the article generated a volley of opinions and counter arguments on the merits and demerits of metamizole, an analgesic drug. In presenting the ‘other side of the story on metamizole’ we refer our readers to a recent article published by Dr Karin Hedenmalm and Dr Olav Spigset in the Pharmacoepidemiology and Prescription section of the European Journal of Clinical Pharmacology (Hedenmalm K, Spigset O (2002): Agranulocytosis and other blood dyscrasias associated with metamizole (dipyrone), Eur J Clin Pharmacol 58: 265-274). This is abstracted below:

Metamizole (dipyrone) is an analgesic compound structurally related to amidopyrine from the phenylpyrazolone group. In the early 1930s, amidopyrine was identified as a cause of agranulocytosis. Soon after metamizole was also associated with agranulocytosis and the risk was suggested to be about 1 in 120 treated patients. This estimate however appeared to be based on potentially biased information from published and unpublished patient series. Because of the risk of agranulocytosis, metamizole has been banned or withdrawn from the market in most industrialised countries but is still available in some countries in Europe including Germany, France and Spain, the far East, Africa and Latin and South America. Of particular intrigue are the Swedish regulatory measures for metamizole. In Sweden all metamizole containing products were first withdrawn in March 1974 due to an estimated incidence of agranulocytosis of 1 in 3000 patients. However, later, data from the International Agranulocytosis and Aplastic Anaemia (IAAA) study put down the risk for agranulocytosis as low as 1.1 cases per million users. Therefore, in September 1995, metamizole was re-approved based on the results from the IAAA study and then later, again suspended in April 1999 based on Swedish adverse drug reactions data, which have now been published. Dr Karin Hedenmalm from the Swedish Medical Products Agency and Dr Olav Spigset from Norway’s St. Olav’s University Hospital have reviewed all reports of metamizole-related blood dyscrasias that were submitted to the Swedish Adverse Drug Reactions Advisory Committee (SADRAC). Based on pharmacy sales data and spontaneous reporting of blood dyscrasias in Sweden, they estimate that the risk of agranulocytosis related to metamizole (dipyrone) appears

<table>
<thead>
<tr>
<th>NSAID</th>
<th>Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Azapropazone</td>
<td>High risk</td>
</tr>
<tr>
<td>Piroxicam</td>
<td>Intermediate risk</td>
</tr>
<tr>
<td>Indomethacin</td>
<td>Intermediate risk</td>
</tr>
<tr>
<td>Ketoprofen</td>
<td>Intermediate risk</td>
</tr>
<tr>
<td>Diclofenac</td>
<td>Intermediate risk</td>
</tr>
<tr>
<td>Naproxen</td>
<td>Intermediate risk</td>
</tr>
<tr>
<td>Ibuprofen</td>
<td>Low risk</td>
</tr>
</tbody>
</table>

Psychiatric events with COX-2 inhibitors:
Prescribers should be aware of the possibility of acute psychiatric-type reactions with COX-2 inhibitors as well as conventional NSAIDs, according to Dr David Coulter, Director of CARM. During the first year of monitoring (up to February 2002) in the Intensive Medicines Monitoring Program (IMMP) 291 reports were received of adverse events associated with celecoxib and 149 reports with rofecoxib. 11 and 2 of these, respectively, were of acute psychiatric events. The reported psychiatric events included confusion, depression, hallucinations, anxiety and ‘thinking abnormal’; 1 patient also experienced an exacerbation of manic-depressive psychosis.
to be at least 1:1439 (95% confidence interval 1:850, 1:4684) prescriptions, a much higher figure than previously estimated. Ninety two percent of the cases of blood dyscrasias occurred during the first 2 months of treatment. Additional risk factors were identified in 36% of the patients. In addition, they report that agranulocytosis was not the only manifestation of metamizole-induced blood dyscrasias; in some of the cases all three haematopoiesis were affected according to bone marrow sample findings. In these cases, the outcome was significantly poorer. Thus the risks of agranulocytosis from the present report seem to be considerably higher than the previously estimated risks from the IAAA study. The authors identify several possible reasons for this difference. For example, in countries where metamizole has been available for several years, the number of susceptibles will decrease because individuals who develop agranulocytosis will discontinue the offending drug. In contrast, countries such as Sweden have a greater population of treatment-naïve individuals. The criteria of fever as a measure of agranulocytosis in the IAAA study also might have affected the choice of cases. Anybody taking metamizole for fever (and not just pain) would therefore not be included as cases in that study. Besides, an unknown proportion of agranulocytosis cases was not included in the IAAA study because the patients either recovered or died before hospital admission. Thus, the differences may be more representative of methodological gaps and do not necessarily represent different results.

The present publication provides evidence for the claims of a high risk of agranulocytosis with metamizole in Swedish patients. The study does not, however, clarify whether Scandinavians are genetically at a greater risk for such reactions. Comparative studies in various countries with more diverse population could help resolve this issue further and until this data is available, other drugs should be considered as first-line analgesics.
Recommendations from the Pre-ICDRA (International Conference of Drug Regulatory Authorities) Workshop on ‘The Impact of Regulation on the Safe Use of Drugs’

The tenth International Conference of Drug Regulatory Authorities (ICDRA) was held this year in Hong Kong. Immediately prior to the conference a satellite workshop was held on “The Impact of Regulation on the Safe Use of Drugs”. There were 57 participants at this event representing 32 Member States.

The objectives of this workshop were to discuss issues relating to the adequate exchange of regulatory information; how to deal with controversial regulatory decisions and how to relate decisions to the interested parties; to identify areas where broader collaboration between Member countries and WHO is necessary; and, to suggest recommendations for the safety session at the main ICDRA.

The workshop was divided into four sessions. The first was devoted to discussions on the current state of information sharing among regulators. Presentations were made from Canada, Ghana and Japan which illustrated some of the differences in pharmacovigilance activities between the better developed drug regulatory authorities and the more recently established ones. There were three themes which appeared to be of common concern. These were the broadening scope of pharmacovigilance including the increasing use of traditional medicines, the need to involve consumers and the need for strengthened collaboration among regulators and international organizations.

The second session concerned the pressures from other regulatory authorities, the media and the pharmaceutical industry. The urgent need for guidelines on crisis management was discussed. A plan needs to be developed for risk management when a drug is marketed in a country. One other topic which emerged from this session was the need for adequate monitoring of antiretrovirals.

The third session dealt with the way in which the pharmacovigilance aspect of regulation interacts with the WHO. A presentation was made by the WHO Programme for International Drug Monitoring on the current status of this programme. Two regulatory authorities, currently contributing to the Programme, spoke of the drawbacks of not having complete data. A number of issues arose during this session. There was a unanimous call for increased transparency in decision-making and the need for earlier information sharing to ensure that decisions are made known to all regulators before they are released to the public. The ICH process was also discussed; there was agreement that WHO should be more actively involved in the standard setting, particularly in the area of the safe use of medicines.

The fourth and final session focused on regulatory issues of traditional medicines and lifestyle drugs. A presentation was made by China on the current status of adverse drug reaction monitoring. It was evident that monitoring the quality of traditional medicines should be an integral part of adverse drug reaction monitoring for traditional medicines. Two presentations were made on special problems with smoking cessation therapies and sildenafil. The political pressure to make these drugs available was discussed.

The recommendations from this workshop were then presented during the session on drug safety monitoring at the tenth ICDRA. The following major recommendations were adopted at the plenary:

1. Regulatory authorities should extend their scope of activities to include: surveillance of medication errors, medical devices, homeopathic products, traditional medicines and natural health products.

2. In order to communicate both developing safety concerns and decisions amongst regulatory authorities before they are made public, a secure web-based communication system should be developed.

3. Post-marketing risk management strategies for products identified as posing a significant risk at the time of initial evaluation should be developed.

4. Regulators should all have crisis management plans and test them regularly.

5. The utility of the WHO Adverse Drug Reaction Reports (ADR)- database should be strengthened by timely reporting of quality data by all participating countries.

6. The WHO ADR- database should be openly accessible to all stakeholders.

7. The special needs for assessing the effectiveness and risk of medicines used in the treatment of HIV/AIDS, particularly in developing countries should be considered a priority for WHO.

8. The current WHO Programme for International Drug Monitoring should be strengthened in its role as the mandated global pharmacovigilance system.
EVENTS & ANNOUNCEMENTS

- A Training Workshop for the Application of ATC/DDD Methodology in Drug Utilization Research will be held in Casablanca, Morocco, 21–22 October, 2002. The workshop will be conducted by the WHO Collaborating Centre for Drug Statistics and Methodology, Oslo.

- The International Federation of Associations of Pharmaceutical Physicians (IFAPP) is announcing the availability of 2 educational grants for post-graduate training in Pharmaceutical Medicine in a European University during the academic year 2003–2004. The grants (5,000 Euros each) are available for young physicians under 40 years of age from countries not affiliated to IFAPP (i.e. the following countries are excluded: Argentina, Australia, Belgium, Brazil, Denmark, Finland, France, Germany, Greece, Indonesia, Ireland, Italy, Japan, Korea, Mexico, The Netherlands, Pakistan, Portugal, Serbia, South Africa, Spain, Sweden, Switzerland, United Kingdom and the United States of America). Application forms may be requested from Ms Caroline Van Galen at the IFAPP secretariat (telephone no. + 31 297 285144, fax no. + 31 297 256046). Completed applications must reach the IFAPP secretariat before December 31st, 2002. An overview of courses in Pharmaceutical Medicine in Europe is available on IFAPP website (http://www.ifapp.org).