WHO PHARMACEUTICALS NEWSLETTER

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

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

No. 4, 2005

News & Issues

This issue comes to you close on the heels of the recently concluded Annual meeting of national pharmacovigilance centres here in Geneva. Over forty countries were represented, with the WHO venue providing the perfect opportunity to promote pharmacovigilance within several public health programmes: of interest were the interactions with HIV /AIDS, malaria, helminths and the tuberculosis programmes. Working group exercises on these topics and the sessions on vaccines, patient safety, and classification systems highlighted the future trends and issues in pharmacovigilance. The guest lecture 'Patient safety: a global challenge' by Sir Liam Donaldson, Chief Medical Officer, United Kingdom and Chair of the World Alliance for Patient Safety, was significant in highlighting the common concerns across professions in promoting patient care. It is clear that future efforts will have to build on collaborations, given the widening scope and expanding role of pharmacovigilance. We take the opportunity to thank all the participants for their enthusiasm and active participation while summarizing the recommendations from three of the working group exercises.

TABLE OF CONTENTS

Regulatory Matters

Safety of Medicines

Feature

Amfetamine

Reintroduced with revised prescribing and patient information

Canada. Health Canada is allowing Shire BioChem Inc.'s mixed-salts amfetamine preparation containing neutral sulfate salts of dextro-amfetamine and amfetamine (Adderall XR) back on the Canadian market following a recommendation from the independent New Drug Committee, who reviewed the suspension of the sale of the drug. Health Canada says that, in accordance with the Committee's recommendations, it will allow the product (Adderall XR) to be reintroduced after steps have been taken, including the revision of the product's prescribing and patient information to reinforce the safe use of the drug and to highlight the safety concerns associated with its use (including the risk of sudden cardiac death in paediatrics). Shire BioChem Inc. has been recommended to issue a `Dear Health Professional' letter that advises of the drug's associated risks, and to support independent continuing medical education for Canadian physicians to strengthen their understanding of issues regarding sudden/cardiac death in paediatrics. Health Canada also states that the agency is committed to enhancing post-marketing surveillance of all stimulants used for attention deficit hyperactivity disorder management, and that Shire BioChem Inc. will be requested to provide the agency with regular safety information. (Readers may recall that in February 2005, Health Canada instructed Shire BioChem Inc. to withdraw their amphetamine preparation (Adderall) due to safety information concerning sudden deaths, heart-related deaths and strokes in children and adults receiving recommended doses of the agent. See WHO Pharmaceuticals Newsletter No. 2, 2005).

Reference:

Dear Health-care Professional' letter from Shire Biochem Inc., 31 August 2005 (http://www.hc-sc.gc.ca).

Atomoxetine

Risk of suicidal thoughts

UK, USA. Atomoxetine (Strattera), is a drug approved for the treatment of Attention Deficit Hyperactivity (ADHD) in paediatric and adult patients. The UK Medicines and Healthcare products Regulatory Agency (MHRA) has issued a Press Release with updated warnings on the risk of suicidal thoughts with atomoxetine (Strattera). According to the Press Release Lilly, the manufacturer of atomoxetine (Strattera) in the UK, has submitted data that do identify an increased risk of suicidal thoughts in children receiving the drug. The MHRA is planning to look into the health risks and benefits of atomoxetine (Strattera). In the mean time, the Agency is advising health-care professionals that patients should be carefully monitored for signs of depression, suicidal thoughts or suicidal behaviour and referred for alternative treatment if necessary. Updated warning will be put on the patient information leaflet (PIL) for atomoxetine (Strattera) about the risk of suicidal thoughts and behaviour.

The United States Food and Drug Administration (US FDA) has directed Eli Lilly, the manufacturer of atomoxetine (Strattera), to include a boxed warning and additional warning statements that alert health-care providers to an increased risk of suicidal thinking in children and adolescents being treated with the drug. The FDA has also decided that a Patient Medication Guide, which will advise patients of the risks associated with atomoxetine (Strattera) and precautions that can be taken, should be distributed to patients when atomoxetine (Strattera) is dispensed. The increased risk of suicidal thinking in children was identified in a combined analysis of 12 short-term (6-18 weeks) placebo-controlled trials (11 in ADHD and 1 in enuresis). The analysis showed a greater risk of suicidal thinking during the first few months of treatment in those receiving atomoxetine (Strattera) compared to placebo-treated patients. The FDA has recommended the following for inclusion in the boxed warning:

- Atomoxetine (Strattera) increases the risk of suicidal thinking in children and adolescents with ADHD.
- Anyone considering the use of atomoxetine (Strattera) in a child or adolescent for ADHD must balance the increased risk of suicidal thinking with the clinical need for the drug.
- Patients who are started on therapy should be observed closely for clinical worsening, suicidal thinking or behaviours, or unusual changes in behaviour.
- Families and caregivers should be advised to closely observe the patient and to communicate changes or concerning behaviours with the prescriber.

A similar analysis in adult patients treated with the drug for either ADHD or major depressive disorder (MDD) found no increased risk of suicidal ideation or behaviour in this age-group.

Reference:

1. *Press Release. The Medicines and Healthcare products Regulatory Agency (MHRA), 29 September 2005 (http://www.mhra.gov.uk).*

2. *Public Health Advisory. United States Food and Drug Administration, 29 September 2005 (http://www.fda.gov).*

Bacitracin, Fusafungine, Gramicidin, Tyrothricin

Locally administered products withdrawn

France. Effective 30 September 2005, the French medicines regulatory agency, *Agence française de securité sanitaire des produits de Santé* (AFSSAPS), has ordered that preparations of the antibiotics bacitracin, fusafungine, gramicidin or tyrothricin, which are locally administered (nasally or by oropharynx route) should be withdrawn from the market due to a lack of therapeutic efficacy. The agency is of the opinion that such a move would also prevent the emergence of strains of antibiotic-resistant bacteria. Two years ago, the agency had ordered the withdrawal of three other antibiotics, framycetin, neomycin and sulfasuccinamide, for similar reasons. These measures are consistent with AFSSAPS' recently completed review of locally administered antibiotics as part of a national and European action programme to promote the proper use of antibiotics.

Reference:
Letter to prescribers. AFSSAPS, 19 July 2005 (http://recherche.sante.gouv.fr).

Cetuximab

Recommendations for electrolyte monitoring

USA. ImClone Systems Incorporated and Bristol-Myers Squibb have issued a 'Dear Health-care Provider' letter to announce that the US labelling for cetuximab (Erbitux) has been revised with recommendations for electrolyte monitoring and longer observation periods following cetuximab infusion, following an increased incidence of hypomagnesaemia in clinical trials. The Warnings section has been updated to recommend a 1-hour observation period following cetuximab infusion, and longer observation periods in patients who have infusion reactions. The Dosage and Administration section has also been updated to advise that patients who have infusion reactions may require longer observation periods. The Precautions and Adverse Reactions sections have been updated with recommendations for electrolyte monitoring during and after cetuximab therapy. These recommendations follow the observation in clinical trials of an increased incidence of hypomagnesaemia associated with cetuximab, alone or in combination with chemotherapy, compared with best supportive care or chemotherapy alone; about half of the cetuximab recipients experienced hypomagnesaemia and 10−15% experienced severe hypomagnesaemia.The companies advise that the time to onset of electrolyte abnormalities has ranged from days to months after cetuximab initiation, and that the time to resolution is not well known.

Reference:
'Dear Health-care Provider' letter from Bristol Myers Squibb Company, 13 September 2005 (http://www.fda.gov).

Duloxetine

Reports of adverse hepatic effects

USA. Eli Lilly and Company has received post-marketing reports of hepatic injury (including hepatitis and jaundice) associated with duloxetine (Cymbalta) use. Some of these reports indicate that patients with pre-existing liver disease who take duloxetine (Cymbalta) may be at increased risk for further liver damage. In view of these reports, the product label which cautioned against using duloxetine (Cymbalta) in patients with substantial alcohol use, has now been revised to extend the caution to include also those patients with chronic liver disease.

***Reference*:**
'Dear Health-care Professional' letter from Eli Lilly and Company, 5 October 2005 (http://www.fda.gov).

Fentanyl transdermal system

Labels updated for safe and appropriate use

Canada. The Canadian labelling for fentanyl transdermal system (Duragesic) has been updated to highlight important Health Canada-endorsed safety information regarding safe and appropriate use of the drug, according to a `Dear Health-care Professional' letter and a Public Advisory issued by Janssen-Ortho (1, 2).

The revised labelling highlights that:

- fentanyl transdermal system (Duragesic) contains a high concentration of fentanyl that has been associated with fatal overdose; consumers should be aware of fentanyl overdose symptoms, and should seek immediate medical attention if such symptoms are noted (2);
- there have been Canadian reports of serious and life-threatening hypoventilation associated with fentanyl transdermal system (Duragesic), and prescribers should be aware of, and monitor patients for, factors that may increase this risk including drug interactions, alcohol and other CNS

depressant use, fever, exposure to external heat sources, use in elderly or debilitated patients, and fentanyl transdermal system (Duragesic) use that is not in accordance with prescribing information (1);

- fentanyl transdermal system (Duragesic) is indicated for the management of persistent, moderate-to-severe, chronic pain that cannot be treated by other means in patients already receiving opioids, and should not be used in opioid-naïve patients (1), or be used for intermittent, short-term or post-operative pain (2);
- fentanyl transdermal system (Duragesic) is not recommended for patients aged < 18 years; there have been Canadian reports of death in children using the product (2);
- there is a potential for the misuse, diversion and abuse of fentanyl transdermal system (Duragesic) patches; there have been reports of death involving misuse and abuse in Canada (1); consumers should be advised to protect fentanyl transdermal system (Duragesic) from misuse or theft, and be made aware of the importance of proper disposal and safe storage of the product.

(See WHO Pharmaceuticals Newsletter No. 3, 2005 for a related Public Health Advisory from the US FDA).

***References**:*

1. 'Dear Health-care Professional' letter from Janssen-Ortho Inc., 13 September 2005 (http://www.hc-sc.gc.ca).

2. Public Advisory. Health Canada, 16 September 2005 (http://www.hc-sc.gc.ca).

Hexavac

Suspended due to concerns about long-term effects against hepatitis B

Europe. The European Medicines Agency has recommended the suspension of the marketing authorization for Hexavac. This is a precautionary measure taken amidst concerns about the vaccine's long-term protection against hepatitis B following the identification of a decreased immunogenicity of the hepatitis B component in the vaccine. Hexavac is a vaccine for infants and children against diphtheria, tetanus, whooping cough (pertussis), hepatitis B virus, polio virus and Hemophilus influenzae type b. The current concern does not affect the protection against diphtheria, tetanus, whooping cough, polio and Hemophilus influenzae type b. Sanofi Pasteur MSD, the marketing authorization holder, has been directed to design a specific surveillance programme to determine whether infant and children, already vaccinated with Hexavac, would need to be revaccinated at a later stage, to ensure long-term protection against hepatitis B.

Reference:

Press release. European Medicines Agency, 15 September 2005 (http://www.emea.eu.int).

Medroxy-progesterone

Loss of bone mineral density

Canada. Health Canada has issued a Public Advisory about recent findings that showed medroxyprogesterone (Depo-Provera) may cause significant bone mineral density (BMD) loss in women. Black-box warnings with these findings have been added to the Canadian product label.

The revised boxed warning section states that:

- medroxyprogesterone (Depo-Provera) has been associated with BMD loss that may not be completely reversible, and BMD loss is greater with increasing duration of use;
- it is unknown if adolescent or early-adulthood use of medroxyprogesterone (Depo-Provera) reduces peak bone mass and increases osteoporotic fracture risk in later life;
- medroxyprogesterone (Depo-Provera) should be used for endometriosis therapy or birth control only if other treatments are unacceptable or unsuitable, and for the shortest duration possible; the benefits and risks of medroxyprogesterone therapy should be regularly re-evaluated in all users.

Other sections of the medroxyprogesterone labelling have also been revised to include relevant information and warnings regarding the risk of BMD.

Reference:

Public Advisory. Health Canada, 30 June 2005 (http://www.hc-sc.gc.ca).

Meloxicam

Juvenile rheumatoid arthritis indication: label updated

USA. The US meloxicam (Mobic) label has been updated to include warnings about non-steroidal anti-inflammatory drug (NSAID)-related cardiovascular (CV) and gastrointestinal (GI) risks following the addition of a juvenile rheumatoid arthritis indication. The revised meloxicam (Mobic) labelling includes a black box warning that states that NSAIDs may

increase the risk of fatal myocardial infarction, CV thrombotic events and stroke, and that the drug is contraindicated for the treatment of perioperative pain in the coronary bypass setting; a strengthened warning has also been added regarding GI adverse events. The Indications section has been updated to advise consumers to consider meloxicam's benefits and risks and other treatment options before using meloxicam, and to use the lowest effective dose for the shortest duration. Similar language highlighting the CV risk has been added under the Warnings heading, and language concerning the risk of GI ulceration, perforation and bleeding has been updated. Warnings of stroke, hypertension and congestive heart failure, and warnings that NSAIDs can cause skin reactions have also been added to the label. Information concerning toxicity and renal injury has moved to the Warnings section from the Precautions section.

Reference:
Mobic adds juvenile rheumatoid arthritis indication, cardiovascular black box warnings. FDA Reports - Pink Sheet - Prescription Pharmaceuticals and Biotechnology, 22 August 2005, 67: 15, No. 34.

Nabumetone

Stronger labelling for renal effects

USA. The US labelling for nabumetone (Relafen) has been revised to include a stronger precaution on the renal effects of the drug. Nabumetone's (Relafen's) revised labelling include dosing recommendations (including maximum starting and daily doses, and dosing adjustments) for patients with moderate or severe renal impairment, and states that caution is required when the drug is prescribed to these patients. Nabumetone's (Relafen's) Clinical Pharmacology and Dosage & Administration sections have been updated to reflect the renal impairment recommendations; updates to the Warnings heading includes the addition of oral corticosteroids as a risk factor for GI bleeding if combined with NSAIDs. GlaxoSmithKline states that a separate labelling revision proposal that reflects the US FDA's NSAID labelling recommendations for cardiovascular and GI risk has been submitted to the agency.

Reference:
Relafen labelling revision includes stronger renal effects precaution. FDA Reports - Pink Sheet - Prescription Pharmaceuticals and Biotechnology, 22 August 2005, 67: 16, No. 34.

Non-selective NSAIDs

No changes to current prescribing practice

Europe. Based on the assessment of available evidence on thrombotic risk associated with non-selective non-steroidal anti-inflammatory drugs (NSAIDs), and pending the ongoing review of other safety issues, the European Medicines Agency's Committee on Medicinal Products for Human Use (CHMP) does not currently recommend any changes to the advice to prescribers and patients. The CHMP highlights that the overall safety profiles of non-selective NSAIDs and the risk factors for each patient should be the basis for prescribing decisions, and that non-selective NSAIDs should be used at the lowest effective dose for the shortest period necessary for symptom control. Non-selective NSAIDs reviewed by the CHMP include diclofenac, etodolac, ibuprofen, indomethacin, ketoprofen, meloxicam, nabumetone, naproxen and nimesulide. In its press release, the Agency notes that the revised prescribing advice adopted in June 2005 for selective COX-2 inhibitors (eg celecoxib, etoricoxib, lumiracoxib and parecoxib) remains unchanged. (The June 2005 advice was based on a review that had identified an increase in the risk of thrombotic adverse cardiovascular reactions such as heart attack or stroke with selective COX-2 inhibitors).

References:
Press Release. European Medicines Agency, 29 July 2005 (http://www.emea.eu.int).

Paroxetine

Potential risk in pregnancy

USA. GlaxoSmithKline (GSK) and the US FDA have notified health-care professionals of changes to the Pregnancy/PRECAUTIONS section of the Prescribing Information for paroxetine (Paxil and Paxil CR Controlled-Release Tablets) to describe the results of a GSK retrospective epidemiologic study of major congenital malformations in infants born to women taking antidepressants during the first trimester of pregnancy. This study suggested an increase in the risk of overall major congenital malformations for paroxetine as compared to other antidepressants. Health-care professionals are advised to carefully weigh the potential risks and benefits of using paroxetine therapy in women during pregnancy and to discuss these findings as well as treatment alternatives with their patients. Paroxetine is indicated for the treatment of major depressive disorder, obsessive-compulsive disorder, panic disorder, social anxiety disorder, generalized anxiety disorder and premenstrual dysphoric disorder.

Reference:
'Dear Health-care Professional' letter from GlaxoSmithKline,

27 September 2005 (http://www.fda.gov).

Thioridazine
Sale discontinued in Canada

Canada. According to Health Canda, thioridazine sales have been discontinued in Canada by 30 September 2005 due to the lack of convincing safety information that supports the continued safe use of the drug as an antipsychotic. The Agency says that thioridazine is associated with QT prolongation that predisposes to potentially fatal cardiac arrhythmia including sudden death and *torsade de pointes*. The Agency states that it has received three reports of death, between 2000 and 2005, that were possibly related to thioridazine. The innovator preparation of thioridazine (Novartis' Mellaril) was voluntarily withdrawn from the Canadian market in July 2001 due to safety concerns, but several other generic thioridazine products continued to be marketed in Canada, says the agency(1).

Health Canada advises (2):

- patients using thioridazine to not stop taking the drug, and to see their health care provider as soon as possible to be switched to an alternative treatment;
- health professionals to switch patients from thioridazine to an alternative therapy at the earliest medically feasible point, individualize the switching strategy for each patient, and gradually reduce the thioridazine dosage over several weeks to prevent cholinergic rebound and the recurrence of symptoms of the underlying condition;
- prescribers to monitor for any potentially occurring phenomena of major relevance, including pharmacokinetic interactions, rebound symptoms, extrapyramidal features (in particular involuntary movement disorders) and cardiac arrhythmia associated with QT prolongation, when switching to an alternate anti-psychotic medications.

Health Canada states that pharmacies will be permitted to continue dispensing remaining thioridazine supplies after 30 September 2005 to allow patients time to switch to another antipsychotic medication. Thioridazine will also be available through the Special Access Programme for patients who can not be adequately managed on alternative therapies, says the agency.

***References*:**

1. Advisories/Warnings. Health Canada, 8 September 2005 (http://www.hc-sc.gc.ca).

2. 'Dear Health-care Professional' letter from Health Canada, 31 August 2005 (http://www.hc-sc.gc.ca).

Anti-TNF alpha products

New measures to prevent activation of latent tuberculosis

France. *Agence française de securité sanitaire des produits de Santé* (AFSSAPS), the French Medicines Agency, has recommended new measures to prevent and treat any activation of latent tuberculosis that might develop during a course of treatment with anti-tumour necrosis factor (anti-TNF) alpha products. The updated advice includes etanercept (Wyeth's Enbrel) and adalimumab (Abbott's Humira), both of which are marketed in France. According to the advice, patients should undergo a skin-reaction test for tuberculosis (TB) before a course of anti-TNF alpha products and during treatment as well, should they present with symptoms of TB; patients should be treated for TB if the tuberculin skin-test reaction is larger than 5 mm (as opposed to the previous advice of 10 mm). The agency advises that a larger dose of isoniazid (5 mg/kg/day as opposed to the previously recommended dose of 4 mg/kg/day) should be used to treat these cases of TB. However, 4mg/kg/day is still the recommended dose if isoniazid is used along with rifampicin.

Reference:
AFSSAPS, 26 July 2005 (http://recherche.sante.gouv.fr).

Beta-2 agonists

Increased risks of asthma-related deaths

Canada. Health Canada is warning Canadians of the possible increased risks of asthma-related deaths associated with the use of a class of asthma drugs known as long-acting β_2-agonists. The advisory includes safety information on the asthma medications formoterol (Novartis' Foradil; AstraZeneca's Oxeze), salmeterol and the combination products of an inhaled corticosteroid with salmeterol (Advair) or formoterol (Symbicort). The advisory is based on a Health Canada analysis of findings from the Salmeterol Multi-center Asthma Research Trial (the SMART study) in the US which showed that salmeterol appeared to increase the risks of asthma-related death and other serious respiratory-related events; data from a SMART post-hoc analysis suggested that these risks may be greater in African-American patients and in patients not using inhaled corticosteroids at study entry. The increased risk with salmeterol may also apply to other long-acting beta-2 agonists such as formoterol although there is no current data to confirm this.

Health Canada recommends that:

- salmeterol and formoterol can only be used with an appropriate dose of inhaled corticosteroid as determined by a physician;
- long-acting β_2-agonists are not a substitute for inhaled or oral corticosteroids;
- salmeterol (Serevent), formoterol (Foradil), or the combination of an inhaled corticosteroid with salmeterol (Advair) should never be used to treat acute or sudden onset of asthma symptoms and attacks;
- the combination product of an inhaled corticosteroid with formoterol (Symbicort) is not indicated for the treatment of sudden asthma symptoms and attacks;
- AstraZeneca's formoterol (Oxeze Turbuhaler) may be used on demand to treat acute symptoms in patients aged ≥ 12 years;
- medical attention should be sought if a patient's asthma medication becomes less effective or if patient needs more inhalations than usual;
- asthma therapy should not be stopped or reduced without first consulting the prescribing physician.

Reference:
Advisories/Warnings. Health Canada, 4 October 2005 (http://www.hc-sc.gc.ca).

Cabergoline

Use linked to gambling

Australia. Four reports of gambling associated with cabergoline (Cabaser) have been reported to the Australian Adverse Drug Reactions Advisory Committee (ADRAC), all of which were received in the past two years, according to the *Australian Adverse Drug Reactions Bulletin*. The affected patients were receiving long-term levodopa, and started their excessive gambling a number of months after cabergoline initiation. In three of these cases, the patients also developed obsessive, abnormal or inappropriate behaviour. In all four cases, the gambling and other behavioural disorders resolved on cabergoline discontinuation. ADRAC advises prescribers to be alert to the development of gambling in patients receiving concomitant levodopa and dopamine receptor agonists.

Reference:
Adverse Drug Reactions Advisory Committee. Pathological gambling with cabergoline. Australian Adverse Drug Reactions Bulletin, August 2005, 24(4):15.

Codeine & hydrocodeine

Akathisia with long-term use

UK. The manufacturers of over-the-counter (OTC) analgesics

that contain codeine and dihydrocodeine have been asked to voluntarily update their labelling and Patient Information Leaflets by the UK Medicines and Healthcare Regulatory Agency (MHRA). The MHRA says that the updated labelling and Patient Information Leaflets will highlight that regular, long-term codeine use may lead to dependence that might cause akathisia and irritability when the drug is discontinued. The agency states that the updated information will advise patients to contact their pharmacist or doctor if their OTC treatment is required for a period of more than three days at a time, and warns that taking an analgesic to alleviate a headache may worsen the symptom if the drug is taken too frequently or for too long.

Reference:
Media Release. Medicines and Healthcare Products Regulatory Agency, 15 August 2005 (http://www.mhra.gov.uk).

Ezetimibe
Reports of muscle pain

Australia. Of the 144 adverse reaction reports associated with ezetimibe (Ezetrol) received by ADRAC since registration of the drug in June 2003, 44 were of muscular disorders, including pain, cramp and weakness. Three of these reports described symptoms that possibly indicated an allergic reaction, and five involved increased serum creatine kinase levels. According to ADRAC, a history of muscular disorders or increased creatine kinase levels in association with statin therapy was reported in 21 patients. In almost half of the 44 cases, the time to onset of muscular disorders was ≤ 2 weeks after ezetimibe initiation, but the time to onset ranged from hours to approximately four months. In five of the 44 cases, along with two published cases, patients received ezetimibe and statin therapy concomitantly; in these cases, the patients had typically received long-term statin therapy, then developed muscle pain or increased serum creatine levels within three months of ezetimibe initiation. Four patients recovered following discontinuation of ezetimibe, and one patient tolerated the withdrawal of ezetimibe and reintroduction of atorvastatin 80 mg/day.

Reference:
Adverse Drug Reactions Advisory Committee. Ezetimibe and muscle disorder. Australian Adverse Drug Reactions Bulletin, August 2005, 24(4):15.

Hydromorphone
Co-ingestion with alcohol harmful

Canada. Health Canada has issued an Advisory to warn of serious health risks associated with the consumption of alcohol while taking any slow-release opioid analgesics, following data from Purdue Pharma that indicated that the co-ingestion of its hydromorphone slow-release formulation (Palladone XL) with any quantity of alcohol may cause serious and potentially fatal complications. The Agency states that when these capsules are taken with alcohol, potentially dangerous levels of hydromorphone are released into the blood quickly (dose-dumping) instead of over 24 hours. Health Canada states that there are no supplies of hydromorphone slow-release formulation (Palladone XL) on the Canadian market. The Agency advises patients receiving other slow-release opioids to be aware that these products may react in a similar way to hydromorphone slow-release formulation when co-ingested with alcohol and to consult their pharmacists if they have any questions. Health Canada advises patients receiving hydromorphone slow-release formulation to contact their doctor with regards to obtaining an alternative drug.

To investigate if the same effect occurs with other slow-release drugs, Health Canada requests that all manufacturers of these products provide information on the interaction between their drug and alcohol; if this is not possible, studies investigating product interactions with alcohol are to be conducted and completed within six months. Health Canada states that the data will be assessed within a three-month period and that further action will be taken if required, but, until then, the issue of possible `dose dumping' associated with alcohol will be temporarily included in the prescribing information for all slow-release opioids.

Reference:
Advisory. Health Canada, 3 August 2005 (http://www.hc-sc.gc.ca).

Ibuprofen
Reports of Stevens-Johnson syndrome

Canada. Health Canada has received four reports of suspected ibuprofen-associated Stevens-Johnson syndrome between 1 January 1973 and 21 February 2005, according to the Canadian Adverse Reaction Newsletter. All four reports were received after April 2001 and involved patients aged 13−34 years who had received ibuprofen 200−1200 mg/day. The time to reaction onset ranged from the day of administration to about 15 days after ibuprofen initiation, and carbamazepine was also identified as a suspect drug in one report. At the time of the reports, the outcome was unknown for one patient and three of the patients had not recovered.

Reference:
Canadian Adverse Reaction Newsletter July 2005, No. 3.

Isotretinoin

Strengthened risk management programme

USA. The US FDA has approved a strengthened isotretinoin (Accutane and generics) risk management programme (iPLEDGE) in an effort to prevent use of the drug during pregnancy; the agency warns that exposure to isotretinoin during pregnancy may significantly increase the risk of congenital disorders. According to the FDA, isotretinoin sponsors will be implementing a programme in which prescribers, pharmacies, wholesalers and patients, who agree to accept specific responsibilities, will be required to register in iPLEDGE before receiving authorization to prescribe, dispense, distribute or obtain isotretinoin; the responsibilities are designed to reduce the risk of exposure to isotretinoin during pregnancy. From 1 November 2005, only iPLEDGE-registered wholesalers will be able to obtain isotretinoin from the manufacturers and only iPLEDGE-registered pharmacies will be able to receive isotretinoin from registered wholesalers. From 31 December 2005, pharmacies will be required to receive iPLEDGE authorization before dispensing an isotretinoin prescription, and only prescriptions from registered prescribers for registered patients will be accepted. Prior to isotretinoin prescription, iPLEDGE prescribers will be responsible for pregnancy counselling of women of child-bearing potential, and for obtaining a negative pregnancy test that will be entered into the iPLEDGE system. Using iPLEDGE, isotretinoin sponsors will implement a system for reporting and collecting information on isotretinoin-related serious adverse events, and monitor compliance and pregnancy rates. The FDA has also approved changes to the current isotretinoin warnings, patient information and informed consent document, to help prescribers and patients identify and manage the risks of depression and psychiatric disorders before and after isotretinoin prescription.

References:

1. *Public Health Advisory. United States Food and Drug Administration, 12 August 2005 (http://www.fda.gov).*
2. *Press Release. United States Food and Drug Administration, 12 August 2005 (http://www.fda.gov*).

Trastuzumab

Addition to chemotherapy increases toxicity

USA. Genentech Inc. has issued a `Dear Health-care Provider' letter to advise that the addition of trastuzumab (Herceptin) to chemotherapy has been associated with increased cardiotoxicity compared with chemotherapy alone in a recent study. In the letter, Genentech presents results from a preliminary analysis of safety data from a Phase III trial, in which 2043 women with operable, human epidermal growth factor receptor 2 (HER2)-over-expressing breast cancer were randomized to receive trastuzumab (Herceptin) in addition to chemotherapy (n = 1019) or chemotherapy alone (*). Among the evaluable patients with adequate heart function who were able to receive trastuzumab (Herceptin), 30.5% had ≥ 1 dose delay because of asymptomatic Left Ventricular Ejection Fraction (LVEF) decrease or heart disorders, and trastuzumab (Herceptin) was discontinued before completion of therapy because of an asymptomatic LVEF decrease in 14.3%, or because of other heart disorders in 4.3%. The 3-year cumulative incidence of New York Heart Association Class III and IV congestive heart failure and cardiac death was significantly increased in the trastuzumab (Herceptin) group compared with the chemotherapy alone group (4.1% vs 0.8%). One cardiac death was reported in the control group, but none were reported in the trastuzumab (Herceptin) group. The company also reports that a final analysis of the cardiac safety data is ongoing.

(*National Surgical Adjuvant Breast and Bowel Project study B-31. Treatment consisted of doxorubicin and cyclo-phosphamide (4 cycles) followed by paclitaxel every three weeks (4 cycles). Patients in the trastuzumab (Herceptin) group received the drug at the approved dose and schedule for one year, during and following paclitaxel).

Reference:

'Dear Health-care Provider' letter from Genentech Inc., August 2005 (http://www.fda.gov).

Vinca alkaloids

Intrathecal administration reported

France. Another case of inadvertent intrathecal vindesine (Eldisine) administration, involving a patient who was supposed to have received IV vindesine and intrathecal methotrexate, has been received, according to Dr Françoise Goebel from the Pharmacovigilance Unit of AFSSAPS. Dr Goebel says that it is difficult to assess the number of such incidents in France, because they are likely to be under-reported. The national drug surveillance system has received four similar cases in the last three years, involving vincristine (n = 3) and vindesine (1). Three of the

incidents occurred in adults and one in a child; despite rapid and appropriate medical care, all four patients died. According to Dr Goebel, in the 20 years to 2002, Lilly Research Laboratories had documented 66 such cases worldwide associated with vindesine, vinblastine or vincristine.
Dr Goebel warns that the scheduling of intrathecal and IV chemotherapy at the same time can cause confusion and may result in medication errors. He advises that it has been recommended that drugs given intravenously and intrathecally should no longer be administered on the same day in children with acute lymphoblastic leukaemia, and says that some adult oncology services administer IV injections in the morning and intrathecal injections in the afternoon. Dr Goebel comments that the intrathecal vinca alkaloid-associated risk of death is known, and is mentioned in the product information for vindesine (Eldisine), vinblastine (Velbé) and vincristine (Oncovin).

Reference:

Goebel F. Accidental intrathecal administration of vinca-alkaloids: risk of death. Vigilances, August 2005, 28:3.

Twenty-eighth Annual Meeting of Representatives of the National Centres participating in the WHO Programme for International Drug Monitoring

Observations from Working Group Exercises

The Twenty-eighth Annual Meeting of Representatives of the National Centres participating in the WHO Programme for International Drug Monitoring was held from 26 to 29 September 2005, in Geneva, Switzerland. In this meeting, working group exercises focused on several key issues in pharmacovigilance including:

- how pharmacovigilance centres react to high profile (drug) withdrawals
- pharmacovigilance in public health programmes
- reporting adverse events following immunization (AEFI)
- developing an international taxonomy for patient safety events
- reporting and learning from patient safety events
- the relevance of the International Classification of Diseases (ICD) in pharmacovigilance.

Below is a summary of key concepts and conclusions from three of the exercises:

1. Improving the effectiveness of pharmacovigilance centres' responses to high profile withdrawals

Regulatory authorities have the responsibility for undertaking several procedures prior to withdrawing a medicine from the market. They must collate and review available data and conduct a risk/benefit assessment. They must also communicate the risk that they identify to prescribers in an adequate manner and identify alternative product options. However, depending on the capacity of the agency, there is much divergence among regulatory agencies in carrying out one or more of these procedures. Well-resourced, and well-established regulatory bodies have access to and capacity to analyse company trial data, local adverse drug reactions (ADR) data, data from the global ADR database and medical literature. Countries with less-developed regulatory systems are restricted by resource and /or capacity constraints. They may be limited to reviewing local data, and although trials may be ongoing in their country they may not have access to the company trial data. They may therefore have to rely on communications from regulatory authorities in developed countries on regulatory actions taken.

In general, from a regulator's perspective, access to drug safety information is often compromised by artificial or inappropriate timelines for reporting, confidentiality requirements, media and government pressure and gaps in human resources and skills.

Inadequate information hampers appropriate and timely regulatory measures, which in turn often erode professional and public confidence in the regulator in particular, and in pharmacovigilance, in general.

Recommendations for improving global-regulatory efficiency should focus around:

- improving information-sharing and multilateral collaborations;
- strengthening regulatory capacity by releasing, in a timely fashion, ADR reports, their evaluation, and all risk-communication material even while still in development;
- promoting electronic exchange and discussion on safety issues of global concerns (eg through Vigimed, E-Drug) and
- undertaking literature review of high risk products and creating a data bank for such literature.

2. Pharmacovigilance in public health programmes

The group identified that there are compelling reasons for including pharmacovigilance into public health programmes including those designed to treat HIV/AIDS, malaria, TB and helminth infections: Many new drugs are used to treat HIV/AIDS, malaria, TB and helminth infections on the basis of efficacy-focused clinical trials of limited duration with little knowledge of their long-term adverse effects. Available data on drug toxicity are mainly from industrialized countries (e.g. in HIV/AIDS treatments), which have a different clinical and operational context in developing countries. Drugs are used in combinations not assessed in developed countries. Life threatening side effects, co-morbidities and co-treatments impact on selection of preferential and alternative drugs

At present few if any public health programmes include a pharmacovigilance component in their design. In several countries that run public health programmes, there are no pharmacovigilance centres and hence, there are no

systematic methods for collecting ADR reports in these countries. In those countries where both systems exist, they often function in parallel, with little communication between the national pharmacovigilance centres and the public health programmes.

United Republic of Tanzania, a case example:
The Tanzanian drug monitoring programme was created as a result of the malaria treatment programme in the country. It started as a process of active collection of ADR reports in the malaria treatment programme, the country now has a fully-fledged pharmacovigilance system and was recognized as a full member of the WHO programme for International Drug Monitoring in 1993.

Recommendations:

- All public health programmes should be required to build pharmacovigilance into their agenda.
- As a first step, the concepts in the ICH E2E guideline on Pharmacovigilance Planning should be used to develop a system for meeting the needs of specific infectious diseases and drug treatment related safety concerns in public health programmes. This guideline describes a method for summarizing the important identified risks of a drug, important potential risks, and important missing information, including the potentially at-risk populations and situations where the product is likely to be used that have not been studied. It proposes a structure for a Pharmacovigilance Plan and sets out principles of good practice for the design and conduct of observational studies.
- The spontaneous reporting system could be used for flagging-off initial concerns which could be further verified using targeted active-surveillance programmes for specific ADR issues. These may be further reinforced with randomized clinical trials, if warranted.
- Where pharmacovigilance centres exist, it is incumbent upon the staff of these centres to establish communications with the relevant staff in the public health programmes, to visit and instruct public health workers in the importance, benefits and methods of reporting an ADR.

3. Vaccines: How to improve AEFI reporting to the WHO global ADR database

There are many barriers to reporting adverse events following immunization programmes. These include: a split between ADR and AEFI pharmacovigilance groups, with the two systems developing as parallel fiefdoms; issues of data ownership; lack of communication between immunization programmes and pharmacovigilance centres; differing objectives (e.g. vaccines programmes may focus more on procurement and storage issues than on pharmacovigilance); lack of education on the importance and benefits of AEFI reporting; insufficient AEFI-oriented elements in current pharmacovigilance training programmes; current taxonomy and definitions of adverse events / reactions being drug (ADR) based; and insufficient vaccine-centres' participation in WHO annual meeting of pharmacovigilance centres.

If this situation is to change there must be an improvement in the following areas:

1. *Political will and commitment.* Officials at higher levels of authority must be involved to introduce AEFI-reporting into national health agendas and there must be active participation of regulators, with appropriate legislation to empower AEFI reporting.
2. *Communication, media and visibility:* There must be improved communication between all partners, across and within systems, nationally and internationally, linking vaccines programmes with pharmacovigilance centres. Vaccine-related topics should be included in popular and reader-friendly journals such as Viewpoint, for increasing awareness about AEFI-issues. Vaccines should be a topic in all WHO annual meetings of national pharmacovigilance centres.
3. *Education and training:* Elements of vaccine-safety and AEFI reporting should be included in the curriculum of undergraduate training of all health professionals. Additional vaccine-safety courses in French, English and in vernacular languages should be organized.
4. *Terminology:* A focus should be on specific AEFI needs and terms. The WHO Collaborating Centre for International Drug Monitoring should analyse the most frequent text terms focusing only on vaccines. The ATC classification system for vaccines should be improved.
5. *Harmonization:* A common reporting system should be developed while retaining a focus on country specific issues. AEFI terms relevant to patient safety should be harmonized. Lot numbers of biological products should be collected in the AEFI reports, as well as details such as private versus publicly provided vaccines for facilitating 'track and search' functions. Common elements and synergies between AEFI and ADR reporting systems should be explored and developed such that both systems benefit mutually.