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:

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

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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.

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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

(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

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