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

Further information on adverse reactions may be obtained from the WHO Collaborating Centre for International Drug Monitoring,
Stora Torget 3,
S-753 20 Uppsala, Sweden
Tel: 46-18-65.60.60
Fax: 46-18-65.60.80
E-mail: sten.olsson@who-umc.org
Internet:http://www.who-umc.org
prepared in collaboration with the WHO Collaborating Centre for International Drug Monitoring, Uppsala, Sweden

Contents ❑

Regulatory matters ❑
Safety of medicines ❑
Feature ❑

No. 6, 2004

News & Issues

This is the final issue of the newsletter for the year 2004. We hope that the information covered has been useful in your work and in keeping abreast of recent developments in drug safety. As stated in the previous issues, we have now established a system for electronic mailing of the newsletter to accommodate those of you who cannot be included in our postal mailing list. To join this list, please send an email to LISTSERV@WHO.INT with the message text: **subscribe WHO-PHN**.

This has been a busy year with many new priority areas emerging in drug safety. The World Alliance of Patient Safety was launched in October and the WHO drug safety programme will work closely with the Alliance, particularly in reporting medication errors and conducting research on the impact of safety measures in promoting patient safety solutions. The issue of safety of medicines in children, with emphasis on off-label use, is also recognized as an important and neglected area that needs to be brought to the attention of WHO.

The Twenty-seventh Annual Meeting of National Centres participating in the WHO Programme for International Drug Monitoring was held from 4 to 6 October, in Dublin, Ireland. We include, in this issue, the observations on the questions discussed by the working groups at the meeting. We hope these observations will stimulate innovative and collaborative approaches to pharmacovigilance. Last, but not least, we wish all our readers good health and happiness in 2005.

TABLE OF CONTENTS

REGULATORY MATTERS

ACTRA-RX AND YILISHEN -- Presence of undeclared sildenafil 1
ADALIMUMAB -- Serious infections if used together with anakinra 1
ANTIDEPRESSANTS -- Label to warn of increased suicidality in children;
Patient Medication Guide to advise on risks and precautions to be taken 1
ATORVASTATIN -- Interaction with grapefruit juice 2
BLACK COHOSH COMBINATION #2; YELLOW DOCK COMBINATION #3 -- Presence of aristolochic acid 2
CELECOXIB -- Withdrawn in Turkey 2
EPOETIN ALFA -- Label change to reflect thrombosis risk 2
ETANERCEPT, INFLIXIMAB -- Reports of serious infections 2
INFLIXIMAB -- Lymphoma warning added to label 2
ISOTRETINOIN -- Enhancement to risk management programme 3
LEVOTHYROXINE SODIUM -- Dysphagia and risk of choking 3
MIFEPRISTONE -- Important labelling changes proposed 3
PERGOLIDE MESYLATE -- Label change: risk of cardiac valvulopathy 4
REMINYL AND AMARYL -- Reports of medication errors 4
VALDECOXIB -- Label updated to warn about skin reactions 4

SAFETY OF MEDICINES

CHOLINESTERASE INHIBITORS -- Reports of cardiac arrhythmias 5
CYCLO-OXYGENASE-2 INHIBITORS -- Plans to review all medicines in this class 5
ETHINYLESTRADIOL / CYPROTERONE -- Increased risk of thrombosis 5
HERBAL MEDICINES -- Cardiovascular ADRs reported to Health Canada 5
INFLUENZA VIRUS VACCINE -- Interactions with drugs 6
MEDROXYPROGESTERONE -- Effect on bone mineral density 6
PAMIDRONATE DISODIUM, ZOLEDRONIC ACID -- Spontaneous reports of osteonecrosis of the jaw 6
SELECTIVE SEROTONIN REUPTAKE INHIBITORS (SSRIs) -- ADRAC reviews use in children and adolescents . 7
TERBINAFINE -- Reports of blood dyscrasias 7
TRICYCLIC ANTIDEPRESSANTS -- Overdose risk 7

FEATURE

Twenty-seventh Annual Meeting of Representatives of the National Centres participating
in the WHO Programme for International Drug Monitoring: Observations from Working Groups 8

ACTRA-RX AND YILISHEN

Presence of undeclared sildenafil

USA. The Food and Drug Administration (FDA) has warned consumers not to purchase or to consume Actra-Rx or Yilishen, two products promoted and offered for sale on websites as dietary supplements for treating erectile dysfunction and enhancing sexual performance in men. The FDA has found that these products contain undeclared prescription strength sildenafil. Sildenafil, when taken together with certain prescription drugs containing nitrates (such as nitroglycerin) may cause a significant lowering of blood pressure to an unsafe level. These drugs should therefore be taken only under medical supervision. The FDA is advising consumers who use Actra-Rx or Yilishen to stop taking these products and to consult their health-care providers regarding erectile dysfunction treatment.

Reference:
FDA Talk Paper, 2 November 2004. Available on the Internet at www.fda.gov

ADALIMUMAB

Serious infections if used together with anakinra

USA. Abbott Laboratories, in consultation with FDA, has updated the prescribing information for adalimumab with new warnings regarding use with anakinra, hypersensitivity reactions and haematologic events. Adalimumab is indicated for the treatment of rheumatoid arthritis. Serious infections were seen in clinical studies with the concurrent use of anakinra and another Tumor Necrosis Factor (TNF)- blocking agent. Since similar toxicities may occur with the concurrent use of anakinra and other TNF blocking agents, and since adalimumab is also a TNF blocking agent, Abbott Laboratories warn that the combination of anakinra with adalimumab is not recommended. In addition, Abbott is also warning that rare but serious anaphylactic and hypersensitivity reactions as well as haematologic reactions including aplastic anaemia have been reported in patients treated with adalimumab; treatment should be discontinued immediately when such hypersensitivity reactions are observed and patients should be advised to seek medical attention if signs and symptoms of haematologic events (e.g. persistent fever, pallor, bruising, bleeding) are noticed.

Reference:
'Dear Health-care Professional' letter from Abbott Laboratories, 5 November 2004. Available on the Internet at www.fda.gov

ANTI-DEPRESSANTS

Label to warn of increased suicidality in children; Patient Medication Guide to advise on risks and precautions to be taken

USA. The FDA has directed manufacturers of all antidepressant drugs to include a boxed warning and expanded warning statements in the labels of these products that alert health-care providers to an increased risk of suicidality in children and adolescents treated with these products and to include additional information about the results of paediatric studies. All drugs included in the general class of antidepressants will have this new boxed and expanded labelling. The risk of suicidality was identified in a combined analysis of short-term placebo-controlled trials of nine antidepressant drugs, including the selective serotonin reuptake inhibitors (SSRIs), in children and adolescents with major depressive disorder (MDD), obsessive compulsive disorder (OCD) or other psychiatric disorders. The analysis showed a greater risk of suicidality during the first few months of treatment in those receiving antidepressants. The average risk of such events on drug was 4%, twice the placebo risk of 2 %. According to the FDA Public Health Advisory, the expanded warning statements will highlight the following:

- Antidepressants increase the risk of suicidal thinking and behaviour (suicidality) in children and adolescents with MDD and other psychiatric disorders.
- Anyone considering the use of an antidepressant in a child or adolescent for any clinical use must balance the risk of increased suicidality with the clinical need.
- Patients on therapy should be observed closely for clinical worsening, suicidality, or unusual changes in behaviour.
- Families and caregivers should be advised to closely observe the patient and to communicate with the prescriber.
- A statement regarding whether the particular drug is approved for any paediatric indication(s) and, if so, which one(s).

The FDA has advised that a Patient Medication Guide (MedGuide) should be given to all patients receiving the drugs to provide information to patients and their families and caregivers about the risk of suicidality in children and adolescents. MedGuides are intended to be distributed by the pharmacist with each prescription or refill of a medication.

Reference:
FDA Public Health Advisory, 15 October 2004. Available on the Internet at www.fda.gov

ATORVASTATIN

Interaction with grapefruit juice

UK. The Summary of Product Characteristics (SPC) for atorvastatin (Lipitor) has been revised to include the interaction between atorvastatin and grapefruit juice. The SPC now states that grapefruit juice contains one or more components that inhibit CYP3A4 and can increase plasma concentrations of drugs metabolised by CYP3A4. Concomitant intake of large quantities of grapefruit juice and atorvastatin is therefore not recommended.

Reference:
SPC for Lipitor, http://emc.medicines.org.uk, 10 November 2004.

BLACK COHOSH COMBINATION #2; YELLOW DOCK COMBINATION #3

Presence of aristolochic acid

Canada. The Health Products and Food Branch Inspectorate in Canada has discontinued the manufacturing authorization for Black Cohosh Combination #2 and Yellow Dock Combination #3 products since they have been found to contain asarum. Asarum is known to produce aristolochic acid, a chemical that can cause cancer, mutations in human cells and end-stage kidney failure (see WHO Pharmaceuticals Newsletter No.3, 2002).

Reference:
Rapid Alert Notification from Health Canada, Reporting System Number T IU 04 388, 30 November 2004.

CELECOXIB

Withdrawn in Turkey

Turkey. The Market Authorization Holder for celecoxib (Celebrex) in Turkey has voluntarily withdrawn celebrex from the Turkish market. The Turkish Human Medicinal Products Advisory Committee had earlier directed that the labels of celecoxib (Celebrex 100 mg and 200 mg) capsules should state that the product may not be used by individuals who have obstructive arterial disorder of the cardiovascular system or the central nervous system.

Reference:
Press Release from the Turkish Ministry of Health and Communication from the Turkish Clinical Pharmacological Society, November 2004.

EPOETIN ALFA

Label change to reflect thrombosis risk

Canada. The Canadian product monograph for epoetin alfa (Eprex) has been revised to include information regarding a possible increased incidence of thrombosis in patients with cancer who have high haemoglobin levels (>120 g/L). The 'Dear Health-are Professional' letter issued by Janssen-Ortho Inc, in consultation with Health Canada, advises that the Contraindications, Warnings, Precautions, Adverse Reactions, Dosage and Administration and Information for the Patient sections have been updated to reflect this safety information.

Reference:
'Dear Health-care Professional' letter from Janssen-Ortho Inc, 13 October 2004. Available on the Internet at www.hc-sc.gc.ca

Reports in WHO-file: Thrombosis 105

ETANERCEPT, INFLIXIMAB

Reports of serious infections

Canada. Health Canada has received a total of 1233 reports of suspected adverse drug reactions (ADRs) to etanercept (Enbrel; n = 536) or infliximab (Remicade; 697), from 1 January 2000 to 31 May 2004, 297 of which were infections. For etanercept, 82 of the 109 reports of infection were considered to be serious, and there were seven deaths; for infliximab, 132 of the 188 reports of infection were considered serious, and there were 14 deaths. The various types of infections reported are detailed below (see table).

Types of serious infections reported to Health Canada

Infection	Etanercept (ADR reports)	Infliximab (ADR reports)
Pneumonia	30	36
Sepsis	15	36
Abscess	10	20
Mycoses	2	14
Cellulitis	3	11
Tuberculosis	2	10
Pyelonephritis or cystitis	8	7
Infectious arthritis	4	7
Encephalitis or meningitis	1	2

Reference:
Canadian Adverse reaction Newsletter 14, No.4, October 2004.

INFLIXIMAB

Lymphoma warning added to US Remicade label

USA. Centocor, Inc[1]. has issued a 'Dear Health-care Professional' letter advising that a warning of malignancies has been added to the US infliximab (Remicade) label. Following the evaluation of safety data on tumour necrosis factor (TNF)-antagonists at a US FDA Arthritis Advisory Committee

meeting in 2003, a malignancy warning has been added to the labels of all TNF-antagonists. The new warning, and the updated Adverse Reactions section of the infliximab (Remicade) prescribing information advise that the incidence of lymphoma is approximately six-fold higher in the combined Crohn's disease/rheumatoid arthritis population from clinical trials of infliximab (Remicade) than in a sex-, age- and race-matched general population. However, they also state that the risk of developing lymphoma has been reported to be up to several-fold higher in the Crohn's disease/rheumatoid arthritis population. The potential role of TNF-antagonist therapy in malignancy development is not known. More recently, Schering Canada[2], in consultation with Health Canada, issued a letter to health-care professionals with similar information, regarding the new warnings added to the infliximab product monograph in Canada. As in the USA, the above information is already included in the Canadian product monographs for TNF-blockers.

References:

1. *'Dear Health-care Professional' letter from Centocor Inc, October 2004. Available on the Internet at www.fda.gov*
2. *'Dear Health-care Professional' letter from Schering Canada Inc, 29 November 2004. Available on the Internet at www.hc-sc.gc.ca*

ISOTRETINOIN

Enhancement to risk management programme

USA. The Food and Drug Administration (FDA) is strengthening the risk minimization action plan (RiskMAP) for isotretinoin, a drug indicated in the treatment of a severe type of acne that is not responsive to other therapies. The enhanced RiskMAP is expected to reduce the risk of birth defects associated with fetal exposure to isotretinoin and to ensure that patients would receive appropriate counselling and testing to prevent the possibility of birth defects. This programme will include, but will not be limited to the following:

- Registration of all prescribers, patients and dispensing pharmacies in a single centralized clearing house.
- Before a registered pharmacy first dispenses the medication for a particular patient, the following will occur:
  - Completion of patient education by the prescriber;
  - An appropriately timed and documented negative pregnancy test prior to dispensing the medication;
  - Completion of the informed consent, education and risk management components by the patient;
  - Electronic or other verification of the above actions.
- For all subsequent prescriptions, the following will occur monthly:
  - Ongoing patient education by the prescriber;
  - Repeated negative pregnancy test within a specified window prior to dispensing;
  - Completion of the education and risk management components by the patient;
  - Electronic or other verification of the above actions.

The isotretinoin sponsors will play a large role in determining compliance and effectiveness of the strengthened RiskMAP including establishing and maintaining a drug-clearing house, monitoring sales, including sales via the internet and evaluating the effectiveness of the programme in reducing and limiting pregnancy exposures.

Reference:

FDA Talk Paper, 23 November 2004. Available on the Internet at www.fda.gov

LEVOTHYROXINE SODIUM

Dysphagia and risk of choking

USA. Jones Pharma Incorporated has issued a 'Dear Health-care Professional' letter advising of changes to the US labelling of levothyroxine sodium (Levoxyl) in response to reports of gagging, choking, 'tablet stuck in throat' and dysphagia in patients taking levothyroxine sodium, usually without water. The US package insert has been revised to include a warning that 'Levoxyl may rapidly swell and disintegrate' resulting in the above-mentioned adverse events. Patients are strongly advised to take Levoxyl with a full glass of water.

Reference:

'Dear Health-care Professional' letter from King Pharmaceuticals Inc, 17 September 2004. Available on the Internet at www.fda.gov

MIFEPRISTONE

Important labelling changes proposed

USA. The FDA has advised important new safety changes to the labelling of mifepristone (Mifeprex, RU-486) approved for the termination of early pregnancy. The existing black box on the product label will be updated with new information on the risk of serious bacterial infections, sepsis, and bleeding and death that may occur following any termination of pregnancy, including use of mifepristone (Mifeprex, RU-486). This revision has been proposed following reports of serious bacterial infections, sepsis, bleeding, ectopic pregnancies that had ruptured, and death. The revised labelling

will provide physicians and patients with important information so that they can respond and possibly prevent rare but serious complications that may occur with any abortion. The Medication Guide and Patient agreement have also been updated to reflect the new safety information. The FDA will continue to monitor the usage of mifepristone (Mifeprex, RU-486) and may take further action.

Reference:
FDA Statement, 15 November 2004. Available on the Internet at www.fda.gov

PERGOLIDE MESYLATE

Label change: risk of cardiac valvulopathy

Canada. Shire BioChem Inc, following discussions with Health Canada, has issued a 'Dear Health-care Professional' letter and a Public Advisory concerning new safety information on pergolide (Permax) and the risk of cardiac valvulopathy. The letter highlights two recent studies that have shown an increased frequency of cardiac valvulopathy associated with pergolide (Permax), compared with non-ergot dopamine agonists. Given the potentially serious nature of these events, the Warnings, Dosage and Administration, Adverse Events, Post-Marketing and Consumer [illegible] cardiovascular evaluation and periodic monitoring for the development of valvular disease or fibrosis are recommended.

Reference:
'Dear Health-care Professional' letter from Shire Biochem Inc, 12 October 2004. Available on the Internet at www.hc-sc.gc.ca

REMINYL AND AMARYL

Reports of medication errors

USA. Janssen Pharmaceutica has issued a 'Dear Health-care Professional' letter[1] and a 'Dear Pharmacist' letter[2] advising of reports of medication errors involving confusion between galantamine (Reminyl) and glimepiride (Amaryl).

These reports include instances where patients received glimepiride (Amaryl), indicated for type 2 diabetes mellitus, in place of galantamine (Reminyl), indicated for mild-to-moderate Alzheimer's-type dementia, and involved various adverse events (AEs), including severe hypoglycaemia and one case of death[1]. These errors appear to have arisen from prescriptions that have been written, interpreted, labelled and/or filled incorrectly due to the similarity in the names of these agents.

In the letter to pharmacists, the company offers the [illegible]

References:
1. *US FDA Safety Alert: Reminyl (galantamine hydrobromide), 28 October 2004. Available on the Internet at www.fda.gov*
2. *'Dear Health-care Professional' letter from Janssen Pharmaceutica Inc, 19 October 2004. Available on the Internet at www.us.janssen.com*

VALDECOXIB

Label updated to warn about skin reactions

Worldwide. Pfizer is updating the valdecoxib (Bextra) label worldwide with information on a rare skin reaction, and has advised of an increase in cardiovascular events in patients undergoing coronary bypass surgery who receive either valdecoxib alone or in combination with parecoxib. Data from spontaneous reports show that the skin reaction has been reported at a greater rate with valdecoxib than with other cyclo-oxygenase-2 inhibitors, and that the risk mainly exists in the first two weeks of valdecoxib therapy.

Reference:
Media Release from Pfizer, 15 October 2004. Available on the Internet at www.pfizer.com