WHO PHARMACEUTICALS NEWSLETTER

World Health Organization

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

The aim of the Newsletter is to disseminate information on the safety and efficacy of pharmaceutical products, based on communications 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.

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This Newsletter is also available on our Internet website:
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This issue records, in addition to other regulatory news, the revision to the package information for antidepressants in Japan; an approval for the use of colchicine in familial Mediterranean fever in the United States of America; and updated safety information for mycophenolic acid. The risk of hearing impairment with isotretinoin, a review of the abnormal behaviour and sudden death with oseltamivir and an increased risk of bleeding with warfarin and aspirin combination are some of the issues discussed under Safety of Medicines. Under Feature there are three items: a brief note on a newly-funded three year project in New Zealand, to scope and pilot a medication error reporting and prevention system; a brief review of reports of acute generalized exanthematous pustulosis (AGEP) with paracetamol in the WHO database for a potential signal;and a summary of adverse drug reaction reports in Sweden with influenza A (H1N1) vaccine.

Several regulatory authorities have licensed H1N1 swine flu pandemic vaccines for their countries. WHO advises all countries administering these vaccines to conduct intensive monitoring for their safety and to report all adverse events. The WHO Collaborating Centre for International Drug Monitoring, the Uppsala Monitoring Centre (UMC) and Swissmedic (Swiss Agency for Therapeutic Products) have developed a new software tool, PaniFlow, for reporting adverse events following immunization. For additional details of this tool visit the UMC website at www.who-umc.org.

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Safety of Medicines

Feature

Antidepressants

Warning about aggression

Japan. The Ministry of Health, Labour and Welfare (MHLW), Japan have warned patients treated with antidepressants, their families and caregivers to pay due attention to any changes in the patient condition during the course of treatment. This warning came following a review of adverse reactions including hostility and aggression associated with selective serotonin reuptake inhibitors (SSRIs) (fluvoxamine maleate, paroxetine hydrochloride hydrate, and sertraline hydrochloride), serotonin and noradrenaline reuptake inhibitors (SNRIs) (milnacipran hydrochloride), tricyclic antidepressants (amitriptyline hydrochloride, amoxapine, imipramine hydrochloride, clomipramine hydrochloride, dosulepin hydrochloride, lofepramine hydrochloride, nortriptyline hydrochloride and trimipramine maleate), tetracyclic antidepressants (setiptiline maleate, maprotiline hydrochloride and mianserin hydrochloride), trazodone hydrochloride and sulpiride.

With regard to adverse reaction reports with SSRIs and SNRIs (reported to the MHLW until the end of March 2009), there have been a total of 39 cases of harmful behaviour to others including injury and potential events, identified from the clinical course; seven cases associated with fluvoxamine maleate, 26 cases with paroxetine hydrochloride hydrate, two cases with sertraline hydrochloride, and four potential cases with milnacipran hydrochloride. However, causality was considered unknown in 35 of the 39 cases.

With regard to adverse reaction reports with tricyclic antidepressants, tetracyclic antidepressants, trazodone hydrochloride and sulpiride (reported until 15 May 2009), there have been a total of 13 cases of harmful behaviour to others including injury and potential events. For 10 out of the 13 cases, causality was considered unknown or it was evaluated that the SSRIs administered concomitantly had a greater effect.

In many cases of the reports reviewed, it was considered that patients with co-morbid disorders such as a depressed state of manic depressive psychosis or schizophrenia developed excitement, aggression or irritability, or exacerbated co-morbid disorders when prescribed antidepressants.

In light of the above findings, marketing authorization holders have been required to revise package inserts of antidepressants, except sulpiride, to include a precaution of careful administration to patients with manic depressive psychosis or an organic brain disorder, those predisposed to schizophrenia, or those with highly impulsive co-morbid disorders. The following statements will also be added to the package inserts: episodes of anxiety, irritation, excitement, panic attack, irritability, hostility, aggression, and impulsivity have been reported; in patients with these symptoms or behavior, exacerbation of underlying disease and harmful behaviour to others have been reported, though causality with the drugs is not clear. For sulpiride, the reported adverse reactions were considered to be the effect of concomitant SSRIs.

References:

Pharmaceuticals and Medical Devices Safety Information No.258, MHLW, June 2009.
(http://www.pmda.go.jp/english/service/pdf/precautions/PMDSI-258.pdf)
Pharmaceuticals and Medical Devices Safety Information No.260, MHLW, August 2009.
(http://www.pmda.go.jp/english/service/pdf/precautions/PMDSI-260.pdf).

Botulinum toxin Type A and Botulinum toxin Type B

Changes to the prescribing information and established drug names

USA. The US Food and Drug Administration (US FDA) has notified health-care professionals that on 31 July 2009, the Agency approved the following revisions to the prescribing information of the botulinum toxin products (Botox, Botox Cosmetic and Myobloc).

- A Boxed Warning highlighting the possibility of experiencing potentially life-threatening distant spread of toxin effect from the injection site after local injection.
- A Risk Evaluation and Mitigation Strategy (REMS) that includes a Medication Guide to help patients understand the risks and benefits of botulinum toxin products.
- Changes to the established drug names to reinforce individual potencies and prevent medication errors. The new drug name to replace "botulinum toxin type A" is OnabotulinumtoxinA (marketed as Botox and Botox Cosmetic). The one to replace " botulinum toxin type B" is RimabotulinumtoxinB (marketed as Myobloc).

The US FDA approved the other botulinum toxin product in this class, AbobotulinumtoxinA (marketed as Dysport), on

29 April 2009 and this product also includes the Boxed Warning and REMS.
Botulinum toxin products have been approved for temporary improvement in the appearance of glabellar lines, treatment of strabismus, blepharospasm, cervical dystonia and primary axillary hyperhidrosis.

(See WHO Pharmaceuticals Newsletter No. 3, 2009 for warnings about distant spread of toxin effects in the USA as well as reports in WHO Global ICSR database).

Reference:
Safety Information, US FDA 3 August 2009 (www.fda.gov).

Clopidogrel

Potential interaction with proton pump inhibitors

Canada (1). Health-care professionals have been warned about the potential interaction of proton pump inhibitors (PPIs) with clopidogrel (Plavix). This potential interaction could lead to a reduction in the level of clopidogrel's active metabolite and therefore, the therapeutic response to clopidogrel may be affected. Clopidogrel is an antiplatelet medicine that is used to prevent atherothrombotic events.

A letter for health-care professionals from Sanofi-aventis Canada Inc. and Bristol Myers Squibb Canada Co. explains that clopidogrel is a pro-drug metabolized by the liver, partly by cytochrome P450 2C19 (CYP2C19), before it can be biologically active in preventing atherothrombotic events. PPIs are used to prevent and treat peptic ulcer and gastroesophageal reflux and may inhibit, to some degree, the activity of CYP2C19. Recent reports in the literature, mainly for omeprazole, suggest a potential interaction with PPIs through CYP2C19 that may reduce the efficacy of clopidogrel. Although the evidence for CYP2C19 inhibition varies within the class, the effect is possibly related to all members of the PPI class.

Health-care professionals have been advised that administration of PPIs or of other drugs that inhibit CYP2C19 should be discouraged in patients taking clopidogrel (Plavix). They have also been recommended to continue to prescribe clopidogrel (Plavix), because this medicine has demonstrated benefits in preventing life-threatening atherothrombotic events that could lead to myocardial infarction or stroke. The Canadian Product Monograph will be revised to include the new safety information.

New Zealand (2). The New Zealand Medicines and Medical Devices Safety Authority (Medsafe) has required the clopidogrel data sheets to be updated, to include information about genetic factors influencing clopidogrel metabolism, specifically in patients with genetically reduced CYP2C19 function. The information discouraging the use of concomitant medicines that inhibit CYP2C19 metabolism, e.g. omeprazole, will also be included as a precaution.

Until further data are available, Medsafe recommends that health-care professionals continue their current prescribing practices for clopidogrel. Medsafe also recommends that an H2-receptor blocker and/or antacid be considered instead of a proton pump inhibitor in patients requiring concomitant treatment with a proton pump inhibitor, where possible.

(See WHO Pharmaceuticals Newsletter No. 4, 2009 for a public statement in Europe on the possible interaction between clopidogrel and proton pump inhibitors).

References:
(1) Advisories, Warnings and Recalls, Health Canada 20 August 2009 (www.hc-sc.gc.ca).
(2) Prescriber Update Vol. 30 No.3, August 2009 (www.medsafe.govt.nz).

Codeine and dihydrocodeine-containing medicines

New advice on OTC analgesics to minimize the risk of addiction

UK. The Medicines and Healthcare products Regulatory Agency (MHRA) announced a package of measures to minimize the risk of overuse and addiction associated with over the counter (OTC) medicines containing codeine and dihydrocodeine (DHC). This follows recent advice from the Commission on Human Medicines (CHM).

The Patient Information Leaflet and labels will state that these products can cause addiction or overuse headache if used continuously for more than three days. In particular, the warning statement "Can cause addiction. For three days use only" will be positioned clearly and prominently on the front of the pack. All indications related to colds, flu, coughs and sore throats, and references to minor painful conditions will be removed. The remaining list of indications will be for the short term treatment of acute, moderate pain which is not relieved by paracetamol,

ibuprofen or aspirin alone. The pack size and advertising will be also regulated. These measures will affect all OTC solid dose medicines containing codeine or DHC including brands, generics and effervescent forms.

Reference:
Safety warnings and messages for medicines, MHRA 2 September 2009 (www.mhra.gov.uk).

Colchicine

New safety information about drug interactions

USA. Oral colchicine has been used for many years as an unapproved drug with no FDA-approved prescribing information, dosage recommendations, or drug interaction warnings.The Agency is notifying health-care professionals that it has now approved the first single-ingredient oral colchicine product (Colcrys) for the treatment of familial Mediterranean fever (FMF) and acute gout flares; the FDA is also sharing information on two previously uncharacterized safety concerns associated with the use of colchicine that were identified during the drug application review by the Agency.

The US FDA analysis has revealed cases of fatal colchicine toxicity reported in certain patients taking standard therapeutic doses of colchicine and concomitant medications that interact with colchicine, such as clarithromycin. The Agency says that these reports suggest that drug interactions affecting the gastrointestinal absorption and/or hepatic metabolism of colchicine play a central role in the development of colchicine toxicity. In addition, the data supporting the safety and efficacy of the product (Colcrys) in acute gout flares demonstrated that a substantially lower dose of colchicine was as effective as the higher dose traditionally used. Moreover, patients receiving the lower dose experienced significantly fewer adverse events compared to the higher dose.

Based on the above, the US FDA has included important safety considerations in the approved prescribing information of the colchicine product (Colcrys). Health-care professionals are advised not to use P-glycoprotein or strong CYP3A4 inhibitors in patients with renal or hepatic impairment who are currently taking colchicine. Patients are advised to consult the Medication Guide for important safety information.

Reference:
Safety Information, US FDA, 30 July 2009 (www.fda.gov).

Etanercept

Risk of uveitis

New Zealand. Medsafe states that a review of spontaneous post-marketing reports indicated that there may be a risk of uveitis associated with the use of etanercept. Etanercept (Enbrel) is a tumour necrosis factor (TNF) inhibitor indicated for the treatment of rheumatoid arthritis, ankylosing spondylitits, juvenile idiopathic arthritis, psoriasis and psoriatic arthritis. The datasheet of etanercept (Enbrel) has been updated to include uveitis as an uncommon adverse reaction.

Reference:
Prescriber Update Vol. 30, No.3 August 2009 (www.medsafe.govt.nz).

Etravirine

Revisions to the prescribing information

USA. The US FDA and Tibotec Therapeutics have notified health-care professionals of revisions to the WARNINGS AND PRECAUTIONS section of the prescribing information for etravirine (Intelence), used in the treatment of HIV-1 infection in combination with other antiretroviral agents. There have been post-marketing reports of cases of Stevens-Johnson syndrome, toxic epidermal necrolysis and erythema multiforme, as well as hypersensitivity reactions characterized by rash, constitutional findings, and sometimes organ dysfunction, including hepatic failure. Health-care professionals are advised to immediately discontinue the treatment with etravirine (Intelence) when signs and symptoms of severe skin or hypersensitivity reactions develop.

Reports in WHO Global Individual Case Safety Reports (ICSR) database, VigiBase:
Etravirine

Number of events:
Stevens Johnson syndrome: 5
Drug hypersensitivity syndrome: 3
Allergic reaction: 3

Reference:
Safety Information, US FDA 27 August 2009 (www.fda.gov).

Fosamprenavir

Potential association of myocardial infarction

Canada. Health-care professionals have been notified of a potential association

between myocardial infarction and exposure to fosamprenavir (PRTELZIR®) in HIV-infected patients. Fosamprenavir is a protease inhibitor used in combination with low-dose ritonavir and other antiretrovirals in the treatment of HIV-1 infection.

According to the Important Safety Information letter from GlaxoSmithKline Inc., a nested case-control study conducted in the French Hospital Database on HIV has reported an association between exposure to fosamprenavir and an increased risk of myocardial infarction (Odds Ratio 1.55 per additional year of exposure; 95% Confidence Interval, 1.20-1.99). This may be related to the propensity for this drug class to raise blood lipids. Health-care professionals are advised to check triglyceride and cholesterol levels prior to initiating therapy with fosamprenavir and at periodic intervals during therapy, as well as to initiate appropriate clinical management of lipid disorders, as required. The company notes that combination antiretroviral therapy is associated with redistribution of body fat (lipodystrophy) in HIV-infected patients. Clinical examination should include evaluation for physical signs of fat distribution. HIV infection itself has been associated with lipid disorders and ischaemic heart disease. The Canadian Product Monograph will be revised to include the new

zafirlukast and zileuton

Revisions to the prescribing information

USA. The US FDA has announced an update to the Precautions section of the prescribing information for the leukotriene inhibitors, montelukast (Singulair), zafirlukast (Accolate), and zileuton (Zyflo and Zyflo CR), to include information about neuropsychiatric events reported in patients using these products. The reported neuropsychiatric events include agitation, aggression, anxiousness, dream abnormalities and hallucinations, depression, insomnia, irritability, restlessness, suicidal thinking and behavior (including suicide), and tremor.

This announcement is an update to the original March 2008 early communication and January 2009 follow-up communication about the ongoing safety review for these leukotriene inhibitors. Montelukast is used to treat asthma, and the symptoms of allergic rhinitis (sneezing, stuffy nose, runny nose, itching of the nose), and to prevent exercise-induced asthma. Zafirlukast and zileuton are used to treat asthma.

The US FDA recommends that patients and health-care professionals should be aware of

(See WHO Pharmaceuticals Newsletter No. 4, 2009 for previous information on neuropsychiatric events with leukotriene inhibitors in Canada and the USA).

Reference:
Safety Information, US FDA 28 August 2009 (www.fda.gov).

Mycophenolic acid

Revisions to the prescribing information

USA. The US FDA and Novartis Pharmaceuticals Corporation have notified health-care professionals that cases of pure red cell aplasia (PRCA) have been reported in patients treated with mycophenolate mofetil (MMF) in combination with other immunosuppressive agents. MMF is metabolized to mycophenolic acid. Mycophenolic acid (Myfortic) is indicated for the prophylaxis of organ rejection in patients receiving allogeneic renal transplants, administered in combination with cyclosporine and corticosteroids.The WARNINGS and ADVERSE REACTIONS sections of the prescribing information for mycophenolic acid (Myfortic) have been revised to reflect this new safety information about PRCA.

PRCA is a type of anaemia in which there is a selective reduction of red blood cell