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 issue includes regulatory decisions taken on antipsychotics, clopidogrel, erlotinib and other medicines and safety information on more than 10 products. The Feature article is on the Inspection of Bio-Equivalence Studies carried out by the WHO Programme for the Prequalification of Medicines. We hope the information will be useful and relevant to you in your work.

The third WHO training course on Pharmacovigilance (for Francophone countries) was held in June 2009 at Rabat, Morocco. This was hosted by the Moroccan Pharmacovigilance Centre. In July 2009, WHO held the third advanced training course in Maputo, Mozambique, for Consultants in Pharmacovigilance for Africa. We will include a report in the next issue. These training courses and workshops have been very important in building capacity and in strengthening ongoing initiatives in pharmacovigilance in sub-Saharan Africa.

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Regulatory Matters

Safety of Medicines

Feature

Antipsychotics

Risk of venous thromboembolic events

UK. The Medicines and Healthcare products Regulatory Agency (MHRA) has advised health-care professionals that antipsychotic use may be associated with an increased risk of venous thromboembolic events (VTE). According to Drug Safety Update, a Europe-wide review of case reports in the UK and worldwide published epidemiological studies on antipsychotics and VTE has concluded that an increase in the risk of VTE with antipsychotics cannot be excluded.

The MHRA says that the product information for health-care professionals and patients for all antipsychotics will be updated across the European Union (EU) to include information about this risk. The product information for antipsychotics clozapine, olanzapine, and aripiprazole already contain warnings about this risk.

Reference:
Drug Safety Update, MHRA, Volume 2, Issue 11, June 2009 (www.mhra.gov.uk).

Clopidogrel

Possible interaction between clopidogrel and proton pump inhibitors

Europe. The European Medicines Agency (EMEA) has issued a public statement saying that the Agency is aware of recently published studies suggesting that clopidogrel may be less effective in patients receiving a proton pump inhibitor (PPI). This could pose an increased risk of thrombotic events, including acute myocardial infarction.

Clopidogrel is an antiplatelet medicine that is used to prevent atherothrombotic events in patients who have had myocardial infarction, ischaemic stroke, or acute coronary syndrome. Clopidogrel is converted from an inactive form to an active form in the body. PPIs are used to prevent and treat heartburn and stomach ulcers. They include omeprazole, esomeprazole, lansoprazole, pantoprazole and rabeprazole. As heartburn and stomach ulcers can occur as side effects of clopidogrel, patients taking clopidogrel often take PPIs to prevent or ease these symptoms.

According to the EMEA, data suggest that a significant interaction might occur between clopidogrel and members of the PPI class of medicines, making clopidogrel less effective when given with these medicines. The Agency's Committee for Medicinal Products for Human Use (CHMP) recommended that the product information for all clopidogrel-containing medicines should be amended to discourage concomitant use of PPI and clopidogrel-containing medicines unless absolutely necessary. The CHMP also recommended that further information is needed in relation to the inhibition of clopidogrel metabolism by other medicines, and in relation to the implications of a genetic variation which results in a small proportion of individuals (so called 'CYP2C19 poor metabolisers') being unable to fully convert clopidogrel to its active form, regardless of interactions with other medicines.

Reference:
Public statement, EMEA, 29 May 2009 (www.emea.europa.eu).

Dextropropoxyphene / propoxyphene-containing medicines

Withdrawal recommended in Europe; warning about fatal overdose in the USA

Europe (1). The EMEA has notified the public of results of a review of the safety and efficacy of dextropropoxyphene-containing medicines. The CHMP concluded that their risks, particularly the risk of potentially fatal overdose, are greater than their benefits. Therefore, the Committee recommended that the marketing authorizations for these medicines be withdrawn across the European Union. Dextropropoxyphene is a painkiller used to treat acute and chronic pain. It has been available for about 40 years, either on its own or in combination primarily with paracetamol, as tablets, capsules, suppositories and solutions for injection.

The EMEA explains that the available data have not provided evidence that dextropropoxyphene-containing medicines are more effective than other alternative painkillers. However, data from forensic centres and national mortality statistics from several Member States showed a significant number of deaths associated with overdose. The withdrawal was recommended because no other adequate measures could be identified to minimize these risks sufficiently. The withdrawal will be gradual for patients to be transferred to appropriate alternative therapies, in line with national recommendations.

USA (2). The US Food and Drug Administration (US FDA) has notified health-care professionals that it is taking several actions to reduce the risk of overdose in patients using pain medications

that contain propoxyphene because of data linking propoxyphene and fatal overdoses. The Agency is requiring manufacturers of propoxyphene-containing products to strengthen the label, including the Boxed Warning, emphasizing the potential for overdose when using these products and to provide a Medication Guide to patients, stressing the importance of using the medicines as directed.

The US FDA states that it plans to further evaluate the safety of propoxyphene and will take additional regulatory action if necessary. The most frequent side effects of propoxyphene include lightheadedness, dizziness, sedation, nausea, and vomiting.

Reference:
(1) Press Release, EMEA, 25 June 2009 (www.emea.europa.eu).

(2) Safety Information, US FDA, 7 July 2009 (www.fda.gov).

Erlotinib

Increased risk of gastrointestinal perforation

Netherlands. The Medicines Evaluation Board (MEB) has warned that patients receiving erlotinib (Tarceva) are at increased risk of developing gastrointestinal perforations when receiving concomitant anti-angiogenic agents, corticosteroids, non-steroidal anti-inflammatory drugs (NSAIDs) and/or taxane based chemotherapy, or who have prior history of peptic ulceration or diverticular disease. The MEB states that erlotinib should be permanently discontinued in patients who develop gastrointestinal perforation.

Erlotinib is indicated for the treatment of patients with locally advanced or metastatic non-small cell lung cancer after failure of at least one prior chemotherapy regimen. The medicine is also indicated for the treatment of patients with metastatic pancreatic cancer, in combination with gemcitabine.

The Summary of Product Characteristics (SPC) will be revised accordingly. In addition, it will be updated with information on bullous, blistering and exfoliative skin conditions including Stevens-Johnson syndrome and toxic epidermal necrolysis, as well as corneal perforation or ulceration.

Reports in WHO Global ICSR database, Vigibase:

Erlotinib

Number of events:
Duodenal ulcer perforated: 2
Gastric ulcer perforated: 2
Intestinal perforation: 17
Bullous eruption: 19
Dermatitis exfoliative: 5
Erythema multiforme: 1
Skin exfoliation: 28
Skin ulceration: 8
Stevens Johnson syndrome: 1
Corneal ulceration including corneal perforation 4

(See WHO Pharmaceuticals Newsletter No. 3, 2009 for new safety information on cases of gastrointestinal perforation, Stevens-Johnson syndrome and corneal perforation with erlotinib in Canada and in the USA).

Reference:
News, Human Medicines, MEB, 29 May 2009 (www.cbg-meb.nl).

Immunosuppressant medicines

Labelling Changes to warn about the risk of BK virus-associated nephropathy

USA. The US FDA is requiring the makers of certain immunosuppressant drugs to update their labelling to reflect that immunosuppressed patients are at increased risk for opportunistic infections, such as activation of latent viral infections, including BK virus-associated nephropathy. The affected medicines are sirolimus (Rapamune), cyclosporine (Sandimmune and generics), cyclosporine modified (Neoral and generics), mycophenolate mofetil (Cellcept and generics), mycophenolic acid (Myfortic). They are used to protect against the rejection of certain organ transplants.

The US FDA conducted analyses of data in its Adverse Event Reporting System (AERS) to characterize the association between BK virus-associated nephropathy and the use of these immunosuppressant drugs. According to the Agency, the occurrence of BK virus-associated nephropathy is primarily observed in renal transplant patients.

Health-care professionals have been alerted that BK virus-associated nephropathy can progress to renal allograft loss and that monitoring for this risk and early intervention, including adjustments in immunosuppression therapy, is very important.

The association of BK virus-associated nephropathy has previously been reported for tacrolimus (Prograf), which is another immunosuppressant. Information about the increased risk for opportunistic infections,

including activation of latent viral infections, is included in the prescribing information for this product.

Reference:
Safety Information, US FDA, 14 July 2009 (www.fda.gov).

Mycophenolate mofetil

Reports of pure red cell aplasia

Canada (1). Health-care professionals have been notified of new safety information regarding reports of pure red cell aplasia (PRCA) in patients treated with mycophenolate mofetil (CellCept) in combination with other immunosuppressive agents. Mycophenolate mofetil is an immunosuppressive agent indicated for the prophylaxis of acute transplant rejection.

According to Health Canada, as of 24 February 2008, 41 cases of PRCA have been reported in patients treated with mycophenolate mofetil (CellCept) in combination with other immunosuppressive agents (tacrolimus, cyclosporine, corticosteroids, azathioprine, sirolimus and alemtuzumab). Based on the preclinical in vivo evidence and post-marketing database, a causal contribution of the medicine on PRCA is considered possible in a few cases. The PRCA may be related to immunosuppression. In some cases, the PRCA was found to be reversible with dose reduction or discontinuation of the product.

Health-care professionals have been advised to consider the contribution of the drugs to PRCA and the prophylaxis of rejection before deciding to discontinue a drug, when PRCA occurs in a patient on multiple immunosuppressants, taking into account that in transplant patients, reduced immunosuppression may place the graft at risk. The Canadian Product Monograph has been revised to include the above safety information.

Netherlands (2). The MEB has communicated the following safety information on mycophenolate mofetil (CellCept).

- Cases of PRCA have been reported in patients treated with mycophenolate mofetil (CellCept) in combination with other immunosuppressants. In some cases, PRCA was reversible with dose reduction or cessation of mycophenolate mofetil.
- Changes to mycophenolate mofetil therapy should only be undertaken under appropriate supervision in transplant recipients in order to minimize the risk of graft rejection.

Reports in WHO Global ICSR database, Vigibase:

Mycophenolic acid

Number of events:
Aplasia, pure red cell: 43

(See WHO Pharmaceuticals Newsletter No. 2, 2009 for the introduction of Medication Guide for mycophenolate mofetil in the USA).

References:
(1) Advisories, Warnings and Recalls, Health Canada, 4 June 2009. (www.hc-sc.gc.ca).
(2) News, Human Medicines, MEB, 4 June 2009 (www.cbg-meb.nl).

Piroxicam

Updated labelling to restrict usage

Canada. Health-care professionals and consumers have been notified that piroxicam should no longer be used to treat short-term pain and inflammation due to an increased risk of serious skin reactions and gastrointestinal problems relative to other similar drugs. Piroxicam is a non-selective NSAID, and is used to relieve pain and inflammation.

Health Canada has conducted a safety review of piroxicam and concluded that the risks associated with its use as a treatment for acute, short-term pain no longer outweigh the benefits relative to other non-selective NSAIDs. Piroxicam can still be prescribed for the symptomatic relief of chronic pain and inflammation in patients suffering from certain types of chronic arthritis (osteoarthritis, rheumatoid arthritis and ankylosing spondylitis).

Health Canada explains that this new safety information affects the product labelling only for piroxicam drugs that are indicated for the treatment of acute pain. The product monographs will be revised accordingly.

Reference:
Advisories, Warnings and Recalls, Health Canada, 25 June 2009 (www.hc-sc.gc.ca).

Varenicline and bupropion

New boxed warning on serious neuropsychiatric events to be required

USA. The FDA has issued a Public Health Advisory, notifying the public that the use of varenicline (Chantix) or bupropion hydrochloride (Zyban), which are used as part of smoking cessation programs,

has been associated with reports of changes in behavior such as hostility, agitation, depressed mood, and suicidal thoughts or actions. The US FDA has directed the manufacturers of varenicline (Chantix) and bupropion (Zyban and generics) to add new Boxed Warnings and develop Medication Guides for patients, highlighting the risk of serious neuropsychiatric symptoms in patients using these products. The same changes to the prescribing information and Medication Guide for patients will also be required for bupropion products (Wellbutrin and generics) that are indicated for the treatment of depression and seasonal affective disorder.

The added warnings are based on the continued review of post-marketing adverse event reports for varenicline and bupropion received by the US FDA. These reports included those with a temporal relationship between the use of varenicline or bupropion and suicidal events and the occurrence of suicidal ideation and suicidal behavior in patients with no history of psychiatric disease.

Health-care professionals have been recommended to advise patients to stop taking varenicline or bupropion and contact a health-care provider immediately if they experience agitation, depressed mood, and any changes in behavior that are not typical of nicotine

(See earlier issues of the WHO Pharmaceuticals Newsletter for worldwide reports of neuropsychiatric events with bupropion (No.3, 2002; No.4, 2004; No. 2, 2007) and with varenicline (Nos,1, 3, 4, 5&6, 2008; No. 1, 2009).

Reference:
Safety Information, US FDA, 1 July 2009 (www.fda.gov).

Zinc-containing intranasal products

Loss of sense of smell

USA. The US FDA has warned consumers and health-care professionals to discontinue the use of three zinc-containing intranasal products sold over-the-counter as cold remedies (Zicam Nasal Gel and Nasal Swab) because they are associated with a long-lasting or permanent loss of sense of smell. According to a Public Health Advisory from the US FDA, these products have not been shown to be effective in the reduction of the duration or severity of cold symptoms. This advisory does not concern oral zinc tablets and lozenges taken by mouth.

The US FDA has received more than 130 reports of anosmia associated with the use of these products. In these reports, many people state that the loss of sense of smell occurred with

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