

WHO PHARMACEUTICALS NEWSLETTER



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.

Contents

Regulatory matters

Safety of medicines

Feature

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TABLE OF CONTENTS

Regulatory Matters

Antipsychotics	1
Clopidogrel	1
Dextropropoxyphene/ propoxyphene-containing medicines	1
Erlotinib	2
Immunosuppressant medicines	2
Mycophenolate mofetil	3
Piroxicam	3
Varenicline and bupropion	3
Zinc-containing intranasal products	4

Safety of Medicines

Cefepime	5
Chloral hydrate and triclofos	5
Fentanyl transdermal patches	5
Golimumab	5
Insulin glargine	6
Latanoprost and rosiglitazone	6
Leukotriene inhibitors	6
Metformin	7
Omalizumab	8
Propylthiouracil	8
Sirolimus	8
Stimulant medications	9
Topical ketoprofen	9
Triamcinolone acetonide	9
Tumour necrosis factor inhibitors	10

Feature

Inspections of Bio-Equivalence Studies	11
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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 (EMA) 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 EMA, 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, EMA, 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 EMA 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 EMA 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.cbq-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 withdrawal, or if they experience suicidal thoughts or behavior.

The US FDA advises that the possible risks of serious adverse events occurring while using varenicline or bupropion should be weighed against the significant health benefits of quitting smoking such as a reduction in the chance of developing lung disease, heart disease, or cancer.

(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 the first dose of the product, although some people report it happened after later doses.

Reference:

Safety Information, US FDA,
16 June 2009
(www.fda.gov).

The Nigerian National Agency for Food and Drug Administration and Control (NAFDAC) publishes a Quarterly Newsletter of its National Pharmacovigilance Centre. To receive your electronic copy of this newsletter, please send an email to:

nafdac_npc@yahoo.com

Cefepime

Update on potential increased mortality

USA. The US FDA has notified health-care professionals that it has finished its analysis of a possible risk of higher death with cefepime, which is a cephalosporin antibacterial, following publication of a study that suggested a higher rate of death in patients treated with cefepime, as compared to patients treated with other β -lactam antibacterials. Cefepime is approved for the treatment of a variety of infections due to susceptible strains of microorganisms. The US FDA states that it performed a meta-analysis based on additional data beyond those included in the publication, and that no statistically significant increase in mortality was observed in cefepime-treated patients compared to comparator-treated patients.

Based on the findings of its meta-analyses, the US FDA has determined that the data do not indicate a higher rate of death in cefepime-treated patients, and cefepime remains an appropriate therapy for its approved indications. The Agency says that it is continuing to review the safety of cefepime.

(See *WHO Pharmaceuticals Newsletter No.6, 2007 about early communication on this subject in the USA*).

Reference:

Safety Information, US FDA, 17 June 2009 (www.fda.gov).

Chloral hydrate and triclofos

Advice on usage

UK. The MHRA has advised health-care professionals that chloral hydrate (Welldorm) and triclofos (Triclofos) are indicated only for the short-term treatment of severe insomnia which is interfering with normal daily life and where other therapies have failed, as an adjunct to non-pharmacological therapies. The Agency says that the product information for these medicines has recently been changed to reflect current clinical practice where they are not first-line options for insomnia. Health-care professionals have also been advised that the use of hypnotics in children and adolescents is not generally recommended, and if used should be under the supervision of a specialist.

Reference:

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

Fentanyl transdermal patches

Warning about accidental child exposure

Canada. Health Canada has warned that health-care professionals, patients and caregivers should be aware of serious medical consequences, including death, that have occurred when people were accidentally exposed to a fentanyl transdermal patch. The fentanyl transdermal system is indicated in the management of persistent, moderate to severe chronic pain that cannot be managed by other means such as opioid combination products or immediate-release opioids.

Examples of accidental exposure include the transfer of a fentanyl transdermal patch while hugging, sharing a bed or moving a patient. In December 2008, Health Canada received a report of suspected accidental fentanyl exposure in a healthy 19-month-old child. It explains that the child was sleeping in the same bed as his mother, who was using a fentanyl patch, and the patch inadvertently became attached to the child. He was taken to hospital and given naloxone 0.01mg/kg intramuscularly as required. His condition improved after treatment.

(See *WHO Pharmaceuticals Newsletter No.4, 2005 for labelling update in Canada*)

Reference:

Canadian Adverse Reaction Newsletter, Health Canada, Volume 19, Issue 3, July 2009 (www.hc-sc.gc.ca).

Golimumab

Risk of serious fungal infections

USA. The US FDA and the makers of golimumab (Simponi) have reminded health-care professionals of the risk of serious fungal infections associated with tumour necrosis factor- α blockers (TNF- α blockers). The US FDA has reported that histoplasmosis and other invasive fungal infections are not consistently recognized in patients taking TNF- α blockers including certolizumab pegol (Cimzia), etanercept (Enbrel), adalimumab (Humira), and infliximab (Remicade). The Agency warns that this has resulted in delays in appropriate antifungal treatment, sometimes even resulting in death.

Health-care professionals have been advised that patients taking TNF- α blockers, which are immunosuppressants, are at risk for developing infections including invasive fungal infections such as histoplasmosis, coccidioidomycosis, blastomycosis, candidiasis, aspergillosis, pneumocystosis, and other opportunistic fungal infections. It has also been advised that for patients who reside or travel in regions where mycoses are endemic, invasive fungal infection should be suspected if they develop a serious systemic illness.

(See WHO Pharmaceuticals Newsletter No.3, 2009 for warning about risk of invasive fungal infections with etanercept in Canada)

Reference:

Safety Information, US FDA, 27 May 2009 (www.fda.gov)

Insulin glargine

Risk of cancer to be investigated

Europe (1). The EMEA's Committee for Medicinal Products for Human Use (CHMP) has finished its review of all available information on a possible relationship between insulin analogues, in particular insulin glargine, and the risk of cancer. The CHMP review concluded that the current evidence was incomplete and the results inconsistent. Since the available data do not provide a cause for concern, the Agency is not recommending any change to the prescribing advice for these products. Insulin glargine is a long-acting insulin analogue and is indicated for the treatment of adults, adolescents and children aged six years or above with diabetes, when

treatment with insulin is required. Because of the limitations of the existing evidence the CHMP has requested the marketing authorization holder to develop a strategy for generating additional information and further research.

USA (2). The US FDA has issued an early communication about safety of insulin glargine (Lantus). The communication states that the Agency is aware of four recently-published observational studies that looked at the use of insulin glargine (Lantus) and the possible risk for cancer in patients with diabetes. Three of the four studies suggest an increased risk for cancer associated with the use of insulin glargine (Lantus). Based on available data, the US FDA recommends that patients should not stop taking their insulin therapy without consulting a physician, since uncontrolled blood sugar levels can have both immediate and long-term serious adverse effects. The US FDA is currently reviewing many sources of safety data for insulin glargine (Lantus), including these observational studies and data from clinical trials. The results will be communicated as appropriate.

References:

1. Press Release, EMEA, 23 July 2009 (www.emea.europa.eu).
2. Safety Information, US FDA, 1 July 2009 (www.fda.gov).

Latanoprost and rosiglitazone

Risk of macular oedema

Australia. The Australian Adverse Drug Reactions Bulletin states that there have been 25

adverse drug reaction reports of drug-associated macular oedema in Australia. The associated medicines are latanoprost (seven reports from a total of 216 for this drug) and rosiglitazone (nine reports from a total of 344). In addition, three each have reported use of an NSAID or a bisphosphonate.

The association between latanoprost and macular oedema as well as rosiglitazone and macular oedema is known and is mentioned in the Product Information documents of these medicines. Latanoprost is a prostaglandin F_{2 α} analogue used as eye drops for the treatment of open angle glaucoma or ocular hypertension. According to the Bulletin, macular oedema is also a risk with other prostaglandin F_{2 α} analogues, although there has been only one report with bimatoprost (from a total of 18 reports) and none with travoprost (from 17 reports).

Health-care professionals have been warned that macular oedema should be suspected with any loss of visual acuity not correctible by pin-hole refraction, and requires prompt specialist evaluation for confirmation of diagnosis and further measures as appropriate.

Reference:

Australian Adverse Drug Reactions Bulletin, Volume 28, Number 3, June 2009 (www.tga.gov.au).

Leukotriene inhibitors

Potential for neuropsychiatric events

Canada (1). Health Canada has informed health-care professionals and consumers about the risk of suicidality and other psychiatric events associated with montelukast. Montelukast sodium (Singulair)

is indicated for the prophylaxis and chronic treatment of asthma in patients aged 2 years and older and for the relief of symptoms of seasonal allergic rhinitis in patients aged 15 years and older when other treatments are not effective or not tolerated. The Canadian product monograph warns patients that, if suicidal thoughts and actions occur, montelukast should be discontinued and a physician or pharmacist should be contacted immediately. It also states that, if severe behaviour and mood-related changes such as agitation including aggressive behaviour occur, a physician or pharmacist should be consulted.

According to Health Canada, until 31 January 2009, there have been 13 adverse reaction reports related to suicidality or self-injury suspected of being associated with the use of montelukast. Eight reports stated that the reaction abated after the dose was reduced or the drug was stopped. The reaction reappeared after the reintroduction of montelukast in one case. In addition, there have been 29 other adverse reaction reports relating to depression, hostility or psychosis suspected of being associated with the use of montelukast. In 19 cases, the reaction abated after the medicine was stopped or the dose was reduced. The reaction reappeared after the reintroduction of montelukast in four cases. No deaths were reported.

USA (2). The US FDA has provided health-care professionals with updated information on the leukotriene inhibitors, montelukast, zafirlukast and zileuton. Montelukast is used to treat asthma, and the symptoms of allergic rhinitis, and to prevent exercise-induced asthma while zafirlukast and zileuton are used to treat asthma. In April 2009,

the Agency completed its review of neuropsychiatric events possibly related to these medicines.

Neuropsychiatric events have been reported in some patients taking montelukast (Singulair), zafirlukast (Accolate) and zileuton (Zyflo and Zyflo CR). The reported neuropsychiatric events include post-market cases of agitation, aggression, anxiousness, dream abnormalities and hallucinations, depression, insomnia, irritability, restlessness, suicidal thinking and behaviour (including suicide), and tremor. Some reports included clinical details consistent with a drug-induced effect.

The US FDA has recommended that patients and health-care professionals should be aware of the potential for neuropsychiatric events with these medications. In addition, the Agency has requested manufacturers to include a precaution in the drug prescribing information (drug labelling).

(See WHO Pharmaceuticals Newsletter No. 2, 2008 for related information posted previously in the USA)

References:

- (1) *Canadian Adverse Reaction Newsletter, Health Canada, Volume 19, Issue 3, July 2009* (www.hc-sc.gc.ca).
- (2) *Safety Information, US FDA, 12 June 2009* (www.fda.gov).

Metformin

Warning about lactic acidosis and dehydration

Australia. The Therapeutic Goods Administration (TGA) and the Adverse Drug Reactions

Advisory Committee (ADRAC) have emphasized the importance of educating patients about how to manage their diabetes and their medications, particularly metformin, when they become acutely unwell. Metformin is contraindicated in acute conditions with a potential to compromise renal function, such as dehydration. A boxed warning for metformin-containing products states that life threatening lactic acidosis can occur due to accumulation of metformin, and that the main risk factor is renal impairment; other risk factors include old age associated with reduced renal function and high doses of metformin (> 2g/day).

According to the Australian Adverse Drug Reactions Bulletin, since 1985, there have been 141 reports of lactic acidosis associated with metformin, 25 of which described a fatal outcome. Many of the reports describe a recent history of diarrhoea, vomiting or gastrointestinal infection prior to the development of acidosis.

The Bulletin states that if patients on metformin develop vomiting and/or diarrhoea, they should see their doctor and consideration should be given to temporarily ceasing metformin until a normal dietary intake can be tolerated. Patients are also advised to consider withholding any concomitant diuretic therapy temporarily since diuretics will exacerbate acute renal impairment in a dehydrated patient.

Reference:

Australian Adverse Drug Reactions Bulletin, Volume 28, Number 3, June 2009 (www.tga.gov.au).

Omalizumab

Early communication about possible cardiovascular and cerebrovascular adverse events

USA. The US FDA has informed health-care professionals that it is evaluating interim safety findings from an ongoing study of omalizumab (Xolair) that suggests an increased number of cardiovascular and cerebrovascular adverse events in a group of patients using omalizumab (Xolair) compared to a group of patients not given the drug (control group). The product is approved for use by adults and adolescents (12 years of age and above) with moderate to severe persistent asthma who test positive for reactivity to a perennial airborne allergen, and whose symptoms are inadequately controlled with inhaled corticosteroids.

According to the Agency, the interim data from the ongoing study, titled Evaluating the Clinical Effectiveness and Long-Term Safety in Patients with Moderate to Severe Asthma (EXCELS), suggests a disproportionate increase in ischaemic heart disease, arrhythmias, cardiomyopathy and cardiac failure, pulmonary hypertension, cerebrovascular disorders, and embolic, thrombotic and thrombophlebitic events in patients treated with omalizumab (Xolair) compared to the control group of patients not given the medicine.

The US FDA states that it is not recommending any changes to the prescribing information for omalizumab and is not advising patients to stop taking the product at this time. Until the evaluation of the study is completed, health-care providers and patients should be

aware of the risks and benefits including this new information. Any new findings will be communicated when its analysis of the interim safety data is complete.

Reference:

Safety Information, US FDA, 16 July 2009
(www.fda.gov).

Propylthiouracil

Increased risk of hepatotoxicity compared to methimazole

USA. The US FDA has issued an FDA alert, notifying health-care professionals of the risk of serious liver injury, including liver failure and death, with the use of propylthiouracil (PTU) in adult and paediatric patients. According to the Agency, reports to the FDA's Adverse Event Reporting System (AERS) suggest that there is an increased risk of hepatotoxicity with PTU when compared to methimazole (MMI). PTU and MMI are both indicated for the treatment of hyperthyroidism due to Graves' disease.

In the AERS database there are 32 cases (22 adult and 10 paediatric) of serious liver injury associated with PTU use. The adult cases included 12 deaths and five liver transplants. Among the paediatric patients, one case resulted in death and six in liver transplants. For MMI, five cases of serious liver injury were identified, and all five cases involved adult patients and three resulted in death.

The US FDA explains that in general, PTU is considered a second-line drug therapy except in patients who are allergic intolerant to methimazole. Rare cases of embryopathy, including aplasia cutis, have been reported with the use of MMI during pregnancy, while no such

cases have been reported with PTU use. Therefore, PTU may be more appropriate for patients with Graves' disease who are in their first trimester of pregnancy.

Health-care professionals have been recommended to reserve PTU use for patients who are in their first trimester of pregnancy, or who are allergic to or do not tolerate methimazole. It has also been advised that PTU should not be used in paediatric patients unless the patient is allergic to or do not tolerate MMI, and there are no other treatment options available.

Reference:

FDA Alert, US FDA, 3 June 2009
(www.fda.gov).

Sirolimus

Clinical trial data suggesting increased mortality

USA. The US FDA has issued an Alert, notifying health-care professionals of clinical trial data that suggest increased mortality in stable liver transplant patients after switching from a calcineurin inhibitor (CNI)-based immunosuppressive regimen to sirolimus (Rapamune). Sirolimus is indicated for the prophylaxis of organ rejection in patients aged 13 years or older receiving kidney transplants. The Agency warns that the safety and efficacy of sirolimus have not been established in liver or lung transplant patients, which is in the Boxed Warning of this medicine. In addition, the current Boxed Warning indicates that the use of sirolimus in combination with tacrolimus was associated with excess mortality and graft loss in a study in de novo liver transplant patients. Many of these patients had

evidence of infection at or near the time of death. The US FDA says that it will continue to examine the data on mortality and other adverse events in this study, and will make further recommendations, as appropriate.

Reference:

FDA Alert, US FDA, 11 June 2009
(www.fda.gov).

Stimulant medications

Ongoing safety review on possible association with sudden death

USA. The US FDA has issued a safety communication about the study data published in the American Journal of Psychiatry on the potential risks of stimulant medications (dexamethylphenidate hydrochloride, dextroamphetamine sulfate, lisdexamfetamine dimesylate, methamphetamine, methylphenidate, amphetamine, pemoline) used to treat Attention-Deficit/Hyperactivity Disorder (ADHD) in children. The study compared the use of stimulant medications in 564 healthy children from across the United States who died suddenly to the use of stimulant medications in 564 children who died as passengers in a motor vehicle accident. Out of the 564 healthy children who died suddenly, 10 were reported to be taking a stimulant medication at the time of death. Out of the 564 healthy children who died in a motor vehicle accident, two were reported to be taking a stimulant medication at the time of death. The study authors concluded that there may be an association between the use of stimulant medications and sudden death in healthy children.

The US FDA states that given the limitations of this study's methodology, it is unable to conclude that these data affect the overall risk and benefit profile of stimulant medications used to treat ADHD in children. Health-care professionals have been advised to follow the current prescribing information including taking a medical history for cardiovascular disease in the child and his or her family and performing a physical exam with a focus on the cardiovascular system.

The US FDA is continuing its review of studies on the risks of stimulant medications used to treat ADHD in children.

Reference:

Safety Information, US FDA, 15 June 2009
(www.fda.gov).

Topical ketoprofen

Risk of photosensitivity reactions

UK. Health-care professionals have been advised about the risk of photosensitivity reactions in users of topical ketoprofen. Ketoprofen gels are licensed for the relief of pain, inflammation, and stiffness associated with non-serious arthritis, sports injuries, sprains, and strains. The MHRA has emphasized that users should avoid direct sunlight, ultraviolet rays, and sunbeds or sunlamps and exercise caution for two weeks after stopping treatment. In addition, ketoprofen should be stopped and medical attention should be sought if skin reactions develop.

Reference:

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

Triamcinolone acetonide

Serious ocular adverse reactions with intravitreal infection

Canada. Health Canada has warned about ocular adverse reactions associated with intravitreal injection of triamcinolone. In Canada, Triamcinolone acetonide as a 40-mg/mL suspension has been authorized for intramuscular and intra-articular administration or for injection into tendon sheaths or ganglia. It is indicated for systemic corticosteroid therapy in conditions such as dermatoses, or rheumatoid arthritis and other connective tissue disorders. Intravitreal or intraocular injection of this product is not authorized.

Health Canada explains that intravitreal injection of triamcinolone has several reported complications. Immediate complications include retinal detachment and vitreous hemorrhage. Complications that develop later include cataract progression, steroid-induced glaucoma and endophthalmitis. A number of ocular adverse reactions following intravitreal injection of triamcinolone in Canada have been reported in scientific literature; they include increased intraocular pressure requiring glaucoma medication (60 cases), cataract progression requiring extraction (12), endophthalmitis (1) and temporary occlusion of the central retinal artery (1). Health Canada says that from 1 January 1973 to 31 January 2009, there has been one report of serious ocular adverse reactions suspected of being associated with combined photodynamic therapy and intravitreal injection of triamcinolone. The case involved a 13-year-old girl in whom

increased intraocular pressure, retinal hemorrhage and reduced visual acuity developed following two injections of triamcinolone given about 3 months apart.

Reference:

Canadian Adverse Reaction Newsletter, Health Canada, Volume 19, Issue 3, July 2009
(www.hc-sc.gc.ca).

Tumour necrosis factor inhibitors

Association with lupus erythematosus

Australia. The TGA and ADRAC have warned about an emerging association between tumour necrosis factor (TNF) inhibitors and drug-induced lupus erythematosus (DILE). TNF inhibitors (infliximab, adalimumab, etanercept) are immunosuppressants approved for indications including rheumatoid and psoriatic arthritis, ankylosing spondylitis and Crohn's disease. The Agency explains that the deficiency of TNF caused by these medicines is known to predispose some patients to TNF inhibitor-induced systemic lupus erythematosus.

According to the Australian Adverse Drug Reactions Bulletin, TNF inhibitors account for 35 of the 87 adverse drug reaction (ADR) reports of DILE or DILE-like symptoms received by the TGA since 2003. There have been 21 SLE-related reports with infliximab (from a total of 269 ADR reports), 10 reports with adalimumab (from a total of 144) and 5 reports with etanercept (from a total of 220).

The Bulletin emphasizes that if a patient on TNF inhibitors develops symptoms suggestive of a lupus-like syndrome and is positive for antibodies against

double stranded DNA, treatment should be discontinued.

Reference:

Australian Adverse Drug Reactions Bulletin, Volume 28, Number 3, June 2009
(www.tga.gov.au).

The June 2009 issue of Swissmedic's Pharmacovigilance Newsletter is available on the Agency's website:

<http://www.swissmedic.ch/aktuell/00003/00998/index.html?lang=de>

The Newsletter is available in German and in French.

Inspections of Bio-Equivalence Studies

Dr A J van Zyl, Prequalification of Medicines Programme, WHO

Background

The United Nations Prequalification of Medicines (PQ) Programme was established in March 2001. The programme is managed by the World Health Organization (WHO).¹ The initial pilot project rapidly expanded from its initial objective of prequalifying a small number of HIV/AIDS medicines, to a programme covering HIV/AIDS, tuberculosis, malaria, influenza and reproductive health products.

Evaluation of medicines in the PQ Programme includes assessment of data and information on safety, efficacy and quality.² In addition, inspections are performed to assess compliance with international norms and standards. The initial focus of inspections was that of finished pharmaceutical product manufacturers - to verify data submitted in product dossiers and to assess compliance with Good Manufacturing Practices (GMP).³ Inspection activities expanded in 2003 to include manufacturers of selected active pharmaceutical ingredients and clinical sites in 2004. Clinical sites including Contract Research Organizations (CROs) are inspected to verify Bio-Equivalence (BE) data submitted for assessment and to assess whether these studies were performed in compliance with Good Laboratory Practices (GLP) and Good Clinical Practices (GCP).⁴

Inspections

Initial inspections showed that in some cases, studies were not done in compliance with GCP and GLP - and that data were not always reliable or even available for verification purposes. This led to some antiretroviral medicines being withdrawn from the list of prequalified medicines.⁵ A letter was issued to all sponsors reminding them of their responsibilities, following which some manufacturers withdrew their product dossiers from the assessment process at that time.

As is the practice in regulatory authorities, the PQ Programme can not inspect every BE study submitted for assessment. Each study is however assessed by a team of assessors and contrary to some regulatory agencies that inspect systems at CROs, the PQ inspections are study specific. This means that a BE study is inspected to verify source data including clinical information and bio analysis. During such an inspection, the implementation of the systems and procedures is inspected and data files are scrutinized and verified against submitted data and calculations. Compliance with GCP and GLP for that particular study is also inspected.

A Standard Operating Procedure (SOP) which forms part of the quality assurance system of the inspection unit is followed to identify which studies are to be inspected. BE studies and CROs are selected based on risk assessment (risk based approach) as recommended in ICH Q9.⁶ Some risk criteria include the type of product (e.g. single component, fixed dose combination), properties of the Active Pharmaceutical Ingredient (API) (e.g. solubility), intra-subject variability (as it has an impact on the study size and number of subjects) and bio analytical method validation. Other triggers relate to data submitted in the dossier that raise concern, and where applicable - the history of compliance with norms and standards and previous inspection outcomes.

A team of inspectors perform each inspection. The team consists of a WHO PQ inspector based in Geneva and a co-inspector appointed by WHO, from a Pharmaceutical Inspection Cooperation Scheme (PIC/S) member country. In all cases, inspectors from the national drug regulatory authority of the country where the inspection is done are invited to participate as observers. In some cases, inspectors from national drug regulatory authorities of developing countries - where prequalified products are procured and supplied - are also invited to participate as observers as part of capacity building and training.

FEATURE

Outcome of inspections

The number of BE studies inspected from 2004 to July 2009 are presented in Table 1.

Table 1. Number of studies

Year	Number of sites inspected for identified studies
2004	6
2005	12
2006	14
2007	14
2008	14
2009	5
Total*	65

* Canada plus USA - 1, China - 1, India - 59, South Africa - 4

As a result of the outcome of the first inspections in 2004, some products were withdrawn from the list of prequalified products.⁵ Non compliances observed over the years included - but not limited to:

- Lack of independence of the Ethics Committee;
- Unreliable clinical data for subjects including electro cardiograms (ECG);
- No source data and raw data files existing ;
- Case Report Forms (CRFs) "missing" or destroyed;
- Unreliable chromatograms for subject sample analyses.

In an attempt to further improve the conduct of studies and compliance with good practices, several training workshops were presented over the years in various countries and regions. These were attended by regulators, sponsors and clinical site staff. Additional guidance for CROs was also developed to further clarify the expected standards of GCP and GLP.⁷

Although the number of inspected studies found to be compliant with GCP generally improved, recent inspections further identified practices that are of extreme concern. These included unreliable data such as:

- Discrepancies between electronic raw data files and data submitted in study reports for assessment;
- Improper manual integration of chromatograms observed during inspections even as "no manual integration" was reported;
- Differences in chromatogram peak areas between the electronic raw data files and the printouts submitted to the WHO;
- Batches that fail when data are calculated from raw data files during inspections (e.g. for Quality Control samples) even as these batches were presented as "passing" with values different from those actually obtained during subject sample analysis;
- Inappropriate bio analytical method validation.

Conclusion

It has become evident that more focused inspections may have to be done to verify source data, electronic raw data files and calculations. The submitted data and reports should be verified and confirmed (by inspectors) against initially obtained sample analysis results and bio-analytical method validation data acquired.

In addition, sponsors should exercise improved monitoring and review of data to assure the quality, reliability and integrity of study data they submit in product dossiers.

Sponsors are reminded that they remain responsible for the data submitted in their product dossiers for assessment - and for the products they eventually place on the market.

References

1. www.who.int/prequal (About prequalification)
2. www.who.int/prequal (Dossier assessments)
3. http://www.who.int/medicines/areas/quality_safety/quality_assurance/production/en/
4. <http://www.who.int/medicinedocs/collect/medicinedocs/pdf/whozip13e/whozip13e.pdf>
5. www.who.int/prequal (Removal of Antiretroviral Products from the WHO List of Prequalified Medicines), 1 September 2004 (News)
6. <http://www.ich.org/LOB/media/MEDIA433.pdf>
7. [http://healthtech.who.int/pq/info_general/documents/TRS937/WHO TRS 937 annex9 eng.pdf](http://healthtech.who.int/pq/info_general/documents/TRS937/WHO_TRS_937_annex9_eng.pdf)

National Pharmacovigilance System in Kenya

Reported by: Dr. Jayesh M. Pandit, Head, Department of Pharmacovigilance.

The Department of Pharmacovigilance at the Pharmacy and Poisons Board (PPB), the National Medicines Regulatory Authority in Kenya has been working actively over the last 4 years to develop a National System for Pharmacovigilance in Kenya.

The National Pharmacovigilance System was formally launched on 9 June 2009, in Nairobi, Kenya. Top representatives from the Ministries of Medical Services and the Ministry of Public Health and Sanitation, including the Directors of both these Ministries graced the occasion. Present were also the Chief Pharmacist, Dr. K. C. Koskei, Deputy Registrar of the PPB Dr. F. M. Siyoi and members of the Board and its Secretariat.

Various stakeholders also attended the meeting- over 70 people drawn from the Division of Pharmacy, Ministry Headquarters, provincial directors of health, provincial nursing officers, provincial pharmacists public health programs representatives, mission facilities, professional societies, research institutions, World Health Organization-Country Office and academia across Kenya.

The launch highlighted the commitment of the Pharmacy and Poisons Board to make safe, efficacious and quality medicines available to all in the country. Prof. Ralph Edwards Director, the Uppsala Monitoring Centre sent a congratulatory note to the PPB and looked forward to welcoming Kenya as a full member of the International Drug Monitoring Program.

The Department of Pharmacovigilance has developed a detailed 5-day training program for all health workers in Kenya as a minimum standard of training on Pharmacovigilance. The training package includes specific trainer's manuals and participant's manuals that will be used to roll out Pharmacovigilance in Kenya. The course equips all health-care workers across the healthcare delivery system with the necessary skills, knowledge and attitude to effectively identify, assess and report adverse drug reactions and take appropriate action, if needed. Ultimately the health-care workers will be inspired to become observant professionals and active reporters in Pharmacovigilance to enhance safety of the Kenyan Population.

It is hoped that other countries, especially in Africa, may use these vast resources in training their teams on Pharmacovigilance, to complement those available from WHO/UMC. The following documents were officially launched at the event:

- ❖ Guidelines for the National Pharmacovigilance System in Kenya
- ❖ Suspected ADR Reporting Form
- ❖ Alert Card
- ❖ Poor Quality Medicinal Product Complaint Form
- ❖ Training and Implementation Guide
- ❖ Trainer's manual
- ❖ Participant's manual.