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 from:

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

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Contents

No. 4, 2010

The US FDA has recently uncovered fraudulent Tamiflu sold over the internet, which put many patients at risk for anaphylaxis. Read about this and other alerts in our regular sections, Safety of Medicines and Regulatory Matters.

This June, representatives from the pharmaceutical industry and regulatory authorities gathered in Beijing to discuss pharmaceutical development on paediatric formulations. This event was the fourth workshop organized by the Prequalification of Medicines Programme (PQP), which provided an open forum for information exchange on the development, formulation and manufacturing of paediatric medicines. The discussions covered technical, safety and ethical topics with an overall positive feedback from the participants.

Around the same time, Singapore's Health Sciences Authority (HAS) hosted the first pharmacovigilance training for ASEAN countries. The 5-day training course was a collaboration with WHO and UMC, and aimed to strengthen pharmacovigilance awareness and capabilities in ASEAN nations and to build future collaborations for medicines safety in the region.

Printed by the WHO Document Production Services, Geneva, Switzerland

TABLE OF CONTENTS

Regulatory Matters

Safety of Medicines

Features

Dextropropoxyphene

Withdrawal

New Zealand. The New Zealand Medicines and Medical Devices Safety Authority (Medsafe) announced that the consents to distribute medicines containing dextropropoxyphene (Capadex and Paradex) in New Zealand will be revoked on 1 August 2010. Dextropropoxyphene is one of the opiates and used to treat chronic moderate pain. This decision follows a review by the Medicines Adverse Reactions Committee (MARC), which concluded that the risks of these medicines outweigh their benefits (See also *WHO Pharmaceuticals Newsletter* No. 2, 2010).

The Best Practice Advocacy Centre has issued the following advice for transferring patients from dextropropoxyphene:

- Most patients can be transferred to full doses of paracetamol alone. If pain relief is not sufficient, the next step is to add a weak opioid such as codeine (or use a combined paracetamol/codeine preparation). Alternatively, codeine alone could be trialed.
- Oxycodone should not be prescribed in place of dextropropoxyphene unless there has been an inadequate response to a weak opioid.

(See WHO Pharmaceuticals Newsletter No. 4, 2009 for recommendation to withdraw the marketing authorizations for dextropropoxyohene-containing medicines in Europe).

Reference:
Media Releases, Medsafe 26 March 2010
Prescriber Update Vol. 31 No. 2 June 2010.
(www.medsafe.govt.nz).

Gemtuzumab ozogamicin

Voluntary withdrawal

USA. The US Food and Drug Administration (US FDA) has announced that Pfizer Inc. will voluntarily withdraw gemtuzumab ozogamicin (Mylotarg) from the United States market. Gemtuzumab ozogamicin (Mylotarg) is indicated for treatment of acute myeloid leukemia (AML). This medicine was approved in May 2000 under the US FDA's accelerated approval program. In 2004, the company began a confirmatory, post approval clinical trial that was designed to determine whether adding gemtuzumab ozogamicin (Mylotarg) to standard chemotherapy demonstrated an improvement in clinical benefit (survival time) to AML patients. The US FDA says that the trial was stopped early when no improvement in clinical benefit was observed, and after a greater number of deaths occurred in the group of patients who received gemtuzumab ozogamicin (Mylotarg) compared with those receiving chemotherapy alone. The Agency also states that at initial approval, the medicine was associated with a serious liver condition called veno-occlusive disease, and this rate has increased in the post-market setting. The US FDA advises that patients who are currently receiving the medicine may complete their therapy following consultation with their health-care professional.

Reference:
News Release, US FDA, 21 June 2010 (www.fda.gov).

Leflunomide

New boxed warning for severe liver injury

USA. The US FDA announced that information on severe liver injury is being added to the Boxed Warning of leflunomide (Arava), following the Agency's review of adverse event reports. The medicine is used to treat rheumatoid arthritis. The warning includes the following.

- Patients with pre-existing liver disease should not receive leflunomide.
- Patients with elevated liver enzymes (ALT greater than two times the upper limit of normal) should not receive leflunomide.
- Caution should be used in patients who are taking other drugs that can cause liver injury.
- Liver enzymes should be monitored at least monthly for three months after starting leflunomide and at least quarterly thereafter.
- If the ALT rises to greater than two times the upper limit of normal while the patient is on leflunomide, leflunomide should be stopped; cholestryamine washout should be begun to speed the removal of leflunomide from the body; and follow-up liver function tests should be conducted at least weekly until the ALT value is within normal range.

The US FDA says that 49 cases of severe liver injury were reported between August 2002

and May 2009. Of the 49 cases, there were 14 deaths.
An additional five patients required a liver transplant and nine patients experienced a life-threatening event. Twenty-three reports described jaundice at the time of diagnosis, 11 reported coagulopathy, and five reported encephalopathy. Other presenting symptoms in these cases included vomiting, rash and/or itching, abdominal pain and fever. Seventeen cases reported normal liver enzymes prior to starting leflunomide. Of the 49 patients, 46 patients were also taking other medications that have been associated with liver injury, including methotrexate, TNF-α blockers, hydroxychloroquine, acetaminophen, non-steroidal anti-inflammatory drugs and statins. In addition, 14 patients had pre-existing liver disease such as active or chronic hepatitis, and/or a history of alcohol abuse. Although many patients who developed severe liver injury were also taking other drugs that can damage the liver, or had pre-existing liver disease, the US FDA concluded that use of leflunomide was associated with the development of severe liver injury in these patients.

Reports in WHO Global ICSR database, Vigibase:

Leflunomide

Number of reports (SOC liver and biliary system disorders, and additional terms containing liver or hepatic): 960

Most reported reactions (number of events):

Hepatic enzymes increased	*186*
SGOT increased	*163*
SGPT increased	*196*
Gamma-GT increased	*62*
Hepatic failure	*61*
Hepatic function abnormal	*331*
Hepatitis	*111*
Hepatocellular damage	*74*
Bilirubinaemia	*68*
Jaundice	*56*

Reference:
FDA Drug Safety Communication, US FDA 13 July 2010 (www.fda.gov).

Long-Acting Beta-Agonists

New recommendations included in labelling

USA. The US FDA announced that Long-Acting Beta-Agonists (LABAs), which are used for the treatment of asthma and chronic obstructive pulmonary disease (COPD), now contain new recommendations on their appropriate use in their drug labels. The new recommendations apply only to the treatment of asthma and do not apply to the use of LABAs for the treatment of COPD. This follows the Agency's decision (in February 2010) to revise the drug labels of LABAs because of an increased risk of severe exacerbation of asthma symptoms in paediatric and adult patients, as well as death in some patients using LABAs for the treatment of asthma. (See *WHO Pharmaceuticals Newsletter* No.2 2010*).*

The new recommendations in the updated labels include the following.

- Use of a LABA alone without use of a long-term asthma control medication, such as an inhaled corticosteroid, is contraindicated in the treatment of asthma.
- LABAs should not be used in patients whose asthma is adequately controlled on low or medium dose inhaled corticosteroids.
- LABAs should only be used as additional therapy for patients with asthma who are currently taking but are not adequately controlled on a long-term asthma control medication, such as an inhaled corticosteroid.
- Once asthma control is achieved and maintained, patients should be assessed at regular intervals and step down therapy should begin (e.g., discontinue LABA), if possible without loss of asthma control, and the patient should continue to be treated with a long-term asthma control medication, such as an inhaled corticosteroid.
- Paediatric and adolescent patients who require the addition of a LABA to an inhaled corticosteroid should use a combination product containing both an inhaled corticosteroid and a LABA, to ensure adherence with both medications.

Health-care professionals are also advised that LABAs should not be started in patients with acutely deteriorating asthma, and that a rescue inhaler, such as an albuterol inhaler, should be prescribed to treat sudden asthma symptoms.

The US FDA states that when LABAs are used according to those new recommendations and the approved drug labels, the benefits of LABAs in improving asthma symptoms outweigh their risks of increasing severe asthma exacerbations and deaths from asthma.

Reference*:*
Safety Information, US FDA 3 June 2010 (www.fda.gov).

Omeprazole

Risk of hypomagnesaemia

New Zealand. Medsafe advised health-care professionals that an association between omeprazole treatment and hypomagnesaemia has been identified, and that they should be alert to the possibility of hypomagnesaemia in patients taking omeprazole and displaying symptoms such as muscle cramps, weakness, irritability or confusion. The data sheets for medicines containing omeprazole will be updated to include information about this association.

Medsafe says that most case reports of hypomagnesaemia have been associated with long-term use of omeprazole at normal doses (20 to 40 mg per day) and magnesium levels normalised after stopping treatment. Reports of hypomagnesaemia were usually also associated with hypocalcaemia, with some patients displaying symptoms of severe hypocalcaemia and hypomagnesaemia (seizures, cardiac arrhythmia, tetany, severe vomiting leading to other electrolyte disturbances and psychiatric symptoms).

***Reference**:*
Prescriber Update Vol.31 No. 2 June 2010 (www.medsafe.govt.nz).

Orlistat

Labelling change due to reports of severe liver injury

USA. The US FDA has announced that it has approved a revised label for orlistat (Xenical) to include new safety information about cases of severe liver injury that have been reported rarely with the use of this medication. Orlistat is used for weight-loss. Xenical (orlistat 120 mg) is available by prescription and Alli (orlistat 60 mg) is sold over-the-counter (OTC) without a prescription. The Agency is also adding a new warning about rare reports of severe liver injury to the OTC label for Alli. This follows the completed safety review by the Agency of reports of severe liver injury in patients taking orlistat. The review identified 13 total reports of severe liver injury with orlistat; 12 foreign reports with Xenical and one US report with Alli. At this time, a cause and effect relationship of severe liver injury with orlistat use has not been established.

Health-care professionals are advised of the following.

- Post-marketing cases of severe liver injury with hepatocellular necrosis or acute hepatic failure have been reported rarely in people using orlistat (Xenical and Alli). Some of these cases resulted in liver transplant or death.
- Weigh the benefits of weight-loss with orlistat (Xenical and Alli) against the potential risks when determining if these medications are appropriate for patients.
- Instruct patients to report any symptoms of hepatic dysfunction (anorexia, pruritus, jaundice, dark urine, light colored stools, or right upper quadrant pain) when using these medications.
- If liver injury is suspected, orlistat and other suspect medications should be discontinued immediately and liver function tests and ALT and AST levels should be obtained.

Reports in WHO Global ICSR database, Vigibase:

Orlistat

Number of reports (SOC liver and biliary system disorders, and additional terms containing liver or hepatic): 598

Most reported reactions (number of events):

Hepatic enzymes increase	*100*
Cholecystitis	*66*
Cholelithiasis	*161*
Gallbladder disorder	*79*
Hepatic function abnormal	*84*

(See WHO Pharmaceuticals Newsletters No.5 2009 for early communication about an ongoing safety review in the USA).

***Reference**:*
Safety Information, US FDA 26 May 2010 (www.fda.gov).

Proton pump inhibitors

Class labelling change due to possible increased risk of fractures of the hip, wrist, and spine

USA. The US FDA announced that it is revising the prescription and over-the-counter (OTC) labels for proton pump inhibitors to include new safety information about a possible increased risk of fractures of the hip, wrist and spine with the use of these medications. Proton pump inhibitors are used to treat conditions such as gastroesophageal reflux disease, stomach and small intestine ulcers, and inflammation of the esophagus. Health-care professionals are advised to consider whether a lower dose or shorter duration of therapy would adequately treat the patient's condition when

prescribing proton pump inhibitors.

The decision on class labelling change is based on the US FDA's review of seven published epidemiological studies, six of which reported an increased risk of fractures of the hip, wrist and spine with proton pump inhibitor use. Some studies found that those at greatest risk for these fractures received high doses of proton pump inhibitors or used them for one year or more. The majority of the studies evaluated individuals 50 years of age or older and the increased risk of fracture primarily was observed in this age group. According to the Agency, it is not clear at this time if the use of proton pump inhibitors is the cause of the increased risk of fractures seen in those studies.

The US FDA states that while the greatest increased risk for fractures in these studies involved people who had been taking prescription proton pump inhibitors for at least one year or who had been taking high doses of the prescription medications, as a precaution, the labelling for the OTC proton pump inhibitors (indicated for 14 days of continuous use) also is being revised to include information about this risk.

Reports in WHO Global ICSR database, Vigibase:

Proton pump inhibitors

Number of reports (SOC musculo-skeletal system disorders, HLT Fracture and HLT No HL-term): 119

Reported reactions (number of events)

Esomeprazole

Fracture	*63*
Fracture healing impaired	*2*
Fracture spontaneous	*5*

Lansoprazole

Fracture	*11*
Fracture pathological	*3*

Omeprazole

Fracture	*27*
Fracture pathological	*5*

Pantoprazole

Fracture	*7*
Fracture healing impaired	*1*
Fracture pathological	*2*
Fracture spontaneous	*1*

Proton pump inhibitors

Fracture	*1*

Rabeprazole

Fracture	*10*
Fracture healing impaired	*1*
Fracture spontaneous	*1*

(See WHO Pharmaceuticals Newsletter No. 2, 2009 for possible risk of fracture in Australia).

Reference:

Safety Information, US FDA 21 April 2010 (www.fda.gov).

Quinine

Warning against the routine use for nocturnal leg cramps in the UK; New risk management plan in the USA

UK (1). The Medicines and Healthcare products Regulatory Agency (MHRA) has warned that quinine should not be considered a routine treatment for nocturnal leg cramps, and should only be considered when cramps cause regular disruption of sleep. Before use for nocturnal leg cramps, the risks should be carefully considered relative to the potential benefits. Quinine should only be considered: when cramps are very painful or frequent; when other treatable causes of cramp have been ruled out; and when non-pharmacological measures have not worked (e.g., passive stretching exercises). After an initial trial of four weeks, treatment should be stopped if there is no benefit. Treatment should be interrupted approximately every three months to reassess the benefit. In patients taking quinine long term, a trial discontinuation may be considered.

In the *Drug Safety Update*, MHRA states that overall efficacy of quinine is modest, based on a meta-analysis of eight randomised placebo controlled trials, which indicated that patients had around 20% fewer cramps in a four-week period (around one episode a week difference) when taking quinine compared with placebo.

With regard to safety of quinine, adverse events may include tinnitus, impaired hearing, headache, nausea, disturbed vision, confusion, flushing and abdominal pain. MHRA advises that treatment should be stopped if these occur. Moreover, thrombocytopenia is a rare but potentially life-threatening adverse reaction associated with quinine. The Agency says that a small number of deaths linked to thrombocytopenia have been reported in patients taking quinine for the treatment of leg cramps, including two cases in the UK Yellow Card database. Health-care professionals are advised that quinine should not be prescribed to patients who have previously experienced any adverse reaction to quinine, including that found in tonic water or other beverages. Patients should be instructed to stop treatment and consult a physician if signs of thrombocytopenia occur, such as unexplained petechiae, bruising, or bleeding. Quinine has a number of potentially significant drug interactions, including with digoxin and

warfarin. It also has significant toxicity in overdose, which can result in death or permanent visual loss.

USA (2). The US FDA has announced that it has approved a Risk Evaluation and Mitigation Strategy (REMS) to warn against the use of quinine sulfate (Qualaquin) for night time leg cramps. Quinine sulfate (Qualaquin) is only approved for the treatment of uncomplicated malaria caused by the parasite Plasmodium falciparum. Quinine sulfate (Qualaquin) is not approved for the treatment or prevention of night time leg cramps. The Agency warns that the use of quinine sulfate (Qualaquin) may result in serious and life-threatening haematological reactions, including serious bleeding due to thrombocytopenia and haemolytic-uremic syndrome/ thrombotic thrombocytopenic purpura, which in some cases may result in permanent kidney damage. In some patients, adverse reactions result in hospitalization and death.

The REMS requires that patients be given a Medication Guide and that the manufacturer issue a Dear Health Care Provider Letter warning of the risk of serious and life-threatening hematologic reactions. Health-care professionals are also advised to discuss with patients the warning signs of thrombocytopenia such as easy bruising, severe nose bleeds, blood in the urine or stool, bleeding gums, and the appearance of unusual purple, brown or red spots on the skin.

The US FDA says that from April 2005 to 1 October 2008, there were 38 U. S. cases of serious adverse events associated with quinine. The majority of patients (25) took quinine to prevent or treat leg cramps or Restless Leg Syndrome; only 1 patient was taking quinine for the treatment of malaria. Among the 38 reports, there were 24 haematologic events, four cardiovascular events, and 10 miscellaneous adverse events such as gastrointestinal symptoms, hearing loss, rash, electrolyte imbalance and drug interaction.

(See WHO Pharmaceuticals Newsletters No. 1, 2007 for warning against off-label use in treating leg cramps in the USA, and No. 4, 2002 for reports of thrombocytopenia in Australia).

References:

(1) Drug Safety Update, MHRA Volume 3, Issue 11, June 2010 (www.mhra.gov.uk).
(2) Safety Information, US FDA 8 July 2010 (www.fda.gov).

Seasonal trivalent influenza vaccination

Status report of investigation into febrile reactions

Australia. The Therapeutic Goods Administration (TGA) has issued the status report as of 2 July 2010 regarding its investigation into febrile reactions in young children following 2010 seasonal trivalent influenza vaccination. According to the TGA, as of 4 June 2010, it had received a total of 1729 Adverse Event. Following Immunization (AEFI) reports concerning the 2010 Southern Hemisphere trivalent influenza vaccine (TIV). These included 1152 reports of fever and 123 reports of convulsions in children under five years. The TGA states that there have been 100 confirmed cases of febrile convulsions in children under the age of five years across Australia, 58 of which were reported from Western Australia. Of the 100 cases, the TIV products FLUVAX or FLUVAX JUNIOR were used in all 66 cases where the brand of the seasonal influenza vaccine was reported. Epidemiological data suggest that those products are associated with febrile reactions in the 4 to 24 hours following vaccine administration at higher rates than documented following seasonal TIV administration in previous years in Australia.

The TGA has concluded that, while epidemiological analyses to date demonstrate an excess of fever and febrile convulsions in children 6 months to 5 years, the overall risk benefit balance of both products (FLUVAX and FLUVAX JUNIOR) remains positive. Nevertheless in view of the signal, the Product Information documents for both products have been revised to include notification of an increase in reports of fever and febrile convulsions in young children during the 2010 Southern Hemisphere influenza season, and warning that the individual risk benefit balance for the use of FLUVAX in children aged less than 5 years should be carefully considered. The TGA recommends reserving the use of TIV to those children under five in whom the risks of a possible febrile reaction or other AEFI are considered to be outweighed by the benefits of vaccination, because the biological basis for the excess cases of fever and febrile convulsions remains unclear.

Reference:

Safety information, Alerts/advisories, TGA 2 July 2010 (www.tga.gov.au).

Sodium valproate and carbapenems

Warning about the interaction

New Zealand. Medsafe advised prescribers to avoid the use of carbapenem antibiotics (such as imipenem, meropenem and ertapenem) in patients taking sodium valproate, because of the clinically significant interaction between carbapenem antibiotics and sodium valproate. The data sheets are being updated to strengthen the warnings about this interaction.

In Europe, the interaction has been reported to result in a 60% to 100% decrease in valproate plasma concentration within two days and reduced therapeutic effect. The underlying mechanism of action is yet to be explained.

(See WHO Pharmaceuticals Newsletter No. 3, 2010 for warning against concomitant use of valproic acid/sodium valproate and carbapenems in the UK.)

Reference:
Prescriber Update Vol. 31 No.2 June 2010. (www.medsafe.govt.nz).

Tramadol

Labelling change in the USA to emphasize the risk of suicide and overdose

New Zealand (1). Health-care professionals have been reminded about the prescribing information for Tramadol. Tramadol is a synthetic opioid analgesic that is indicated for the treatment of moderate to severe pain. Tramadol inhibits the reuptake of serotonin and noradrenaline in addition to its opioid action. Tramadol should not be used in patients:

- with acute intoxication with alcohol, hypnotics, analgesics, opioids or psychotropic medicinal products;
- who are receiving monoamine oxidase inhibitors or have taken them in the past 14 days;
- with epilepsy not adequately controlled by treatment;
- with severe renal impairment (creatinine clearance <10 mL/min).

Medsafe warns that although tramadol causes less respiratory depression and addiction than codeine or morphine, it may increase the risk of nausea and vomiting, sedation and dizziness. Tramadol can induce convulsions and increase the potential for selective serotonin re-uptake inhibitors, tricyclic antidepressants, antipsychotics and other seizure threshold lowering agents to cause convulsions. Tramadol is known to cause Serotonin Syndrome when used concomitantly with other medicines that increase serotonin levels.

According to the *Prescriber Update*, as of 14 April 2010, the Centre for Adverse Reactions Monitoring (CARM) had received 162 reports associated with tramadol use. The reports include cases of Serotonin Syndrome, seizures, hyponatraemia, respiratory depression and hypotension in association with tramadol use. There have also been reports of increased INR and/or bleeding when used concomitantly with warfarin.

USA (2). Ortho-McNeil-Janssen and the US FDA notified health-care professionals of changes to the prescribing information for tramadol to emphasize the risk of suicide for patients who are suicidal or addiction-prone and patients who are taking tranquilizers or antidepressant drugs as well as to warn of the risk of overdosage. According to the Dear Healthcare Professional letter, tramadol-related deaths have occurred in patients with previous histories of emotional disturbances or suicidal ideation or attempts, as well as histories of misuse of tranquilizers, alcohol, and other CNS-active drugs. Tramadol may be expected to have additive effects when used in conjunction with alcohol, other opioids or illicit drugs that cause central nervous system depression. Serious potential consequences of overdosage with tramadol are central nervous system depression, respiratory depression and death. Tramadol has mu-opioid agonist activity, can be abused and may be subject to criminal diversion.

References:
(1) Prescriber Update Vol. 31 No. 2 June 2010 (*www.medsafe.govt.nz*).
(2) Safety Information, US FDA, 25 May 2010 (*www.fda.gov*).

Varenicline tartrate

Changes to Product Monograph, including warnings about neuropsychiatric adverse events and hypersensitivity reactions

Canada. Health-care professionals have been notified of changes to the Product Monograph for varenicline tartrate (CHAMPIX), including the addition of a Boxed Warning regarding neuropsychiatric adverse events. Varenicline tartrate (CHAMPIX) is indicated for smoking-cessation treatment in adults in conjunction with smoking-cessation counseling. The letter issued for health-care

professionals states that there have been continuing post-marketing reports of serious neuropsychiatric symptoms, such as depressed mood, agitation, aggression, hostility, changes in behaviour, suicide related events and worsening of pre-existing psychiatric disorder in patients treated with varenicline tartrate (CHAMPIX). These events have occurred in patients with and without pre-existing psychiatric disorder. Some reported cases may have been complicated by the symptoms of nicotine withdrawal in patients who stopped smoking. Alcohol intake may also increase the risk of patients experiencing psychiatric adverse events during treatment with varenicline tartrate (CHAMPIX). Patients are advised to stop treatment with the medicine and contact their health-care provider immediately if they have neuropsychiatric symptoms or behaviours that are not typical for the patient. There have also been post-marketing reports of somnolence, dizziness, loss of consciousness, seizures or difficulty concentrating. Therefore, patients are advised not to engage in potentially hazardous activities, such as driving a car or operating dangerous machinery until they know how they may be affected by varenicline tartrate (CHAMPIX).

Moreover, there have been post-marketing reports of hypersensitivity reactions, such as rare life-threatening angioedema events requiring urgent medical attention and rare severe cutaneous reactions, including Stevens-Johnson syndrome and erythema multiforme. Patients should immediately stop treatment with varenicline tartrate (CHAMPIX) and seek emergency medical care if they experience any signs or symptoms of severe skin/hypersensitivity reactions.

The changes to the Product Monograph also includes two dosing options approved for varenicline tartrate (CHAMPIX). Following one week titration, the dose may be increased to a maximum of 1.0 mg twice daily or remain at 0.5 mg twice daily.

(See earlier issues of the WHO Pharmaceuticals Newsletter for worldwide reports of neuropsychiatric events with varenicline: Nos. 1, 3, 4, 5 & 6, 2008; Nos. 1, 4, 2009).

Reference:

Advisories, Warnings and Recalls, Health Canada
3 June 2010
(www.hc-sc.gc.ca).

Acitretin

Reminder of the risks associated with treatment

New Zealand. Medsafe reminded health-care professionals of the risks associated with acitretin. Acitretin is a synthetic aromatic analogue of retinoic acid that is indicated for the treatment of severe psoriasis, disorders of keratinisation and other dermatoses responsive to etretinate. Acitretin is an active metabolite of etretinate.

Medsafe advised that acitretin is highly teratogenic and is contraindicated in pregnant women and nursing mothers. It should not be used in women of childbearing potential unless prescribing conditions are met. If acitretin is used in a woman of childbearing potential, pregnancy must be avoided for two years following discontinuation of therapy. Strict contraception must be used for one month prior to, during and for 24 months after treatment. In addition, alcohol must be avoided during and for two months after treatment due to an interaction that increases the concentration of etretinate. Etretinate is also highly teratogenic and has a longer half life than acitretin.

Acitretin is also contraindicated in patients with severely impaired hepatic or renal function and in patients with chronic abnormally elevated blood lipids. Hepatic function, serum cholesterol and serum triglycerides should be assessed prior to starting acitretin treatment and regularly during therapy. In patients receiving acitretin, concomitant administration of vitamin A and other retinoids must be avoided due to the risk of hypervitaminosis A. Combined use of tetracyclcines or methotrexate with acitretin must also be avoided.

Reference:
Prescriber Update Vol. 31 No. 2 June 2010 (www.medsafe.govt.nz).

Angiotensin Receptor Blockers

Ongoing safety review for cancer risk

USA. The US FDA has announced that it is conducting a review of angiotensin receptor blockers (ARBs) after a recently published study suggested use of ARBs may be associated with a small increased risk of cancer. ARBs are used in patients with high blood pressure and other conditions. The published study was a meta-analysis combining cancer-related findings from several clinical trials. The study reported the frequencies of new cancer occurrence to be 7. 2% for patients receiving ARBs compared to 6.0% for those not receiving ARBs (risk ratio = 1. 08,95% Confidence Interval: 1.01-1.15). No statistically significant difference in cancer deaths was noted.

The review is ongoing. The US FDA states that at this time, the benefits of ARBs continue to outweigh their potential risks. The Agency recommends that health-care professionals continue to use ARBs as recommended in their product labels. Patients should not stop taking their medication unless told to do so by their health-care professional.

Reference:
FDA Drug Safety Communication, US FDA 15 July 2010 (www.fda.gov).

H1N1 pandemic vaccines and antiviral

Reports of suspected adverse reactions

Australia. The TGA announced suspected adverse reactions to the H1N1 influenza vaccine, Panvax®, reported to the TGA from 30 September 2009 when the national immunization began to 30 April 2010. The TGA concludes that Panvax® is a safe, effective vaccine for prevention of the H1N1 influenza.

According to the Agency, as at 30 April 2010, a total of 1773 suspected side effects have been reported following vaccination with Panvax® in Australia. To that date, approximately 8. 7 million doses of Panvax® and over 370 000 doses of Panvax Junior® had been distributed in Australia. The great majority of reported side effects have been mild and common problems such as headache, gastrointestinal upset, soreness, swelling, or redness at the injection site. Of the suspected side effects reported, 156 were related to Panvax Junior®, and the majority of these reports were of fever (129) and/or vomiting (75).

The TGA also addresses 10 reported cases of Guillain-Barré syndrome (GBS) and states that based on all evidence available, there is no evidence of an increased rate of GBS in people receiving Panvax® compared with that normally seen in the community.

Reference:
Safety information, Alerts/advisories, TGA, 17 June 2010 (www.tga.gov.au).

Intravenous paracetamol

Risk of accidental overdose

UK. The MHRA has advised health-care professionals to exercise caution when prescribing and administering intravenous paracetamol 10 mg/ml solution for infusion (Perfalgan) to ensure that the correct dose is given, especially in infants and neonates**.** The medicine is indicated for the short-term treatment of pain and fever, when there is a clinical need of paracetamol administration intravenously.

According the *Drug Safety Update*, up to 31 May 2010, 23 cases of accidental overdose with intravenous paracetamol 10 mg/ml solution for infusion (Perfalgan) have been reported worldwide in children younger than one year, one of which was fatal. In the UK, there have been seven reports of overdose in infants and neonates. In most of these cases, a 10-fold overdose was reported.

The MHRA explains that occurrence of accidental overdose was due to confusion between the prescription in mg and administration in ml. The MHRA also emphasizes that the recommended dose depends on the weight of the patient, and that the dosing schedule is up to four infusions a day with a minimum of 4 hours between each administration, 6 hours for those with renal impairment. For infants and children who weigh less than 33 kg, the 50 ml vial should be used for administration.

In order to avoid overdose, intravenous paracetamol should not be given concomitantly with oral paracetamol, including combination products.

Reference:
Drug Safety Update, MHRA Volume 3, Issue 12, July 2010 (www.mhra.gov.uk).

Methylphenidate

Product information updated

New Zealand. The Medicines Adverse Reactions Committee (MARC) has recommended that the New Zealand data sheets of methylphenidate be updated for treating children. New contraindications include:

- diagnosis or history of severe depression, anorexic disorders, suicidal tendencies, psychotic symptoms, severe mood disorders, mania, schizophrenia, psychopathic/borderline personality disorder;
- pre-existing cardiovascular disorders;
- pre-existing cerebrovascular disorders.

In addition, patients should be carefully monitored as follows:

- blood pressure should be recorded at every dose adjustment and then at least every six months; pulse should also be recorded.
- height, weight and appetite should be recorded at least every six months. Patients who are not gaining height or weight as expected may need a treatment break.
- patients who develop symptoms suggestive of heart disease should undergo prompt specialist cardiac evaluation.
- prescribers and pharmacists should look out for signs of diversion, misuse and abuse of methylphenidate.

Medsafe warns that methylphenidate can cause or worsen some psychiatric disorders such as depression, suicidal thoughts, hostility, anxiety, agitation, psychosis and mania. Psychiatric well being should therefore be monitored in patients being treated with methylphenidate. The long-term effects of methylphenidate treatment in children are not fully understood.

Reference:
Prescriber Update Vol. 31 No. 2 June 2010 (www.medsafe.govt.nz).

Olmesartan

Ongoing safety review regarding the possible association with increased cardiovascular-related death

USA. The US FDA has announced that it is evaluating data from two clinical trials in which patients with type 2 diabetes taking olmesartan (Benicar), an angiotensin II receptor blocker, had a higher rate of death from a cardiovascular cause (heart attack, sudden death or stroke) compared to patients taking a placebo. The Agency also says that other controlled clinical trials evaluating olmesartan (Benicar) and other angiotensin II receptor blockers have not suggested an increased risk of cardiovascular-related death.

The review is ongoing and the US FDA has not concluded that olmesartan (Benicar) increases the risk of death. The Agency states that it currently believes that the benefits of olmesartan (Benicar) in patients with high blood pressure continue to outweigh its potential risks.

***Reference**:*
FDA Drug Safety Communication, US FDA 11 June 2010. (www.fda.gov).

Pregabalin

Suicidal ideation and attempt

Canada. Health Canada advised that health care professionals, patients and caregivers should be aware of suicidal ideation and attempt suspected of being associated with pregabalin. In Canada, pregabalin is indicated for the management of neuropathic pain associated with diabetic neuropathy, postherpetic neuralgia and pain associated with fibromyalgia in adults.

According to Health Canada, from the date of marketing in July 2005 to 15 December 2009, there were 16 reports of suicidal ideation and one report of suicide attempt suspected of being associated with the use of pregabalin. Seven of the 16 cases included a positive dechallenge (abatement of symptoms of suicidality upon stopping or reducing the dosage of pregabalin) and one case included a positive rechallenge (reappearance of symptoms after reintroduction of pregabalin). Confounders identified in some of the cases included psychiatric disorders, history of depression and suicidal ideation, post-traumatic stress disorder and use of psychotropic medications. Health Canada also states that patients with chronic pain are at increased risk of depression, which may lead to suicidal ideation and attempt, and so the indication for taking pregabalin in these patients may also be a confounding factor.

Reference:
Canadian Adverse Reaction Newsletter Volume 20, Issue 3 Health Canada, July 2010 (www.hc-sc.gc.ca).

Rivastigmine transdermal patch

Risk of medication errors

UK. MHRA warned that case reports of medication errors and inappropriate use of the rivastigmine transdermal patch have been reported, some of which resulted in overdose and required admission to hospital. Rivastigmine (Exelon) transdermal patch is indicated for the symptomatic treatment of mild to moderately severe Alzheimer's dementia. According to the *Drug Safety Update*, the most frequently reported causes were lack of patch removal and application of more than one patch at the same time. Other causes were: application of the patch to non-recommended sites; patch application to the same area for several weeks; cutting the patch into several pieces; and dose errors in prescribing or dispensing.

MHRA's advice for health-care professionals are as follows.

- Symptoms of rivastigmine overdose include nausea, vomiting, diarrhoea, hypertension and hallucinations; bradycardia and/or syncope, associated with malaise or falls, may also occur.
- In case of suspected overdose, all rivastigmine patches should be removed immediately and no further patch should be applied for the next 24 hours.
- It is important to instruct patients and caregivers on the proper use of the transdermal patch, particularly that:
  - Only one patch should be applied per day to healthy skin on the upper or lower back, upper arm or chest.
  - Only one patch should be applied per day to healthy skin on the upper or lower back, upper arm or chest.
  - The patch should be replaced by a new one after 24 hours, and the previous day's patch must be removed before application of a new patch to a different skin location.
  - Application to the same skin location within 14 days should be avoided to minimise skin irritation.
  - The patch should not be cut into pieces.

(See WHO Pharmaceuticals Newsletter No. 3, 2010 for serious adverse events related to medication errors/misuse in Canada).

Reference:
Drug Safety Update, MHRA Volume 3, Issue 11, June 2010. (www.mhra.gov.uk).

Zoledronic acid

Reports of adverse effects on renal function

New Zealand. Medsafe advised prescribers that zoledronic acid is associated with reports of renal impairment and renal failure, especially in patients with pre-existing renal dysfunction. In New Zealand, zoledronic acid 5 mg injection (Aclasta) is indicated for the prevention or treatment of

osteoporosis and the treatment of Paget's Disease of the bone. Zoledronic acid 4 mg injection (Zometa) is indicated for the treatment of osteolytic, osteoblastic and mixed bone metastases of solid tumour in cancer of the breast or prostate, and in the treatment of hypercalcaemia of malignancy. The data sheets for both products contain warnings about renal impairment and renal failure.

According to *Prescriber Update*, as of August 2009, there had been 139 worldwide suspected reports of renal impairment or renal failure associated with zoledronic acid 5 mg (Aclasta). The majority of cases were reported in patients with pre-existing medical conditions (advanced age, renal impairment, concurrent or preceding dehydration), or who had concurrent treatment with nephrotoxic agents such as NSAIDs and/or diuretics). Health-care professionals are advised about the following points.

- Creatinine clearance should be measured before each dose.
- Aclasta should not be used in patients with a creatinine clearance < 35 mL/min.
- Transient increases in serum creatinine may be greater in patients with underlying impaired renal function.
- Monitoring renal function should be considered, particularly in at-risk patients.
- Zoledronic acid should be used with caution with other medicines that could impair renal function.
- Health-care professionals should ensure that all patients, especially the elderly and those receiving diuretics, are adequately hydrated prior to receiving zoledronic acid.
- Zoledronic acid infusions should be administered over at least 15 minutes.

(See WHO Pharmaceuticals Newsletter No. 3, 2010 for warnings about renal impairment and renal failure in the UK and reports in WHO Global ICSR database.)

Reference:

Prescriber Update Vol. 31 No. 2 June 2010. (*www.medsafe.govt.nz*).

Fraudulent Tamiflu

Counterfeit product sold on Internet

USA. The US FDA notified consumers and health-care professionals about a potentially harmful product sold as "Generic Tamiflu" over the Internet. The Agency's tests revealed that the fraudulent product does not contain Tamiflu's active ingredient, oseltamivir, but cloxacillin, an ingredient in the same class of antibiotics as penicillin. The Agency warns that patients who are allergic to penicillin products are at risk of experiencing similar reactions from cloxacillin. This includes anaphylaxis with symptoms that include difficulty breathing, chest tightness, swelling of the throat or tongue, hives, dizziness, loss of consciousness, or a rapid or weak pulse.
The US FDA advises that consumers can be confident that the National Association of Boards of Pharmacy Verified Internet Pharmacy Sites Seal, also known as VIPPS Seal, gives a seal of approval to pharmacy sites that apply and meet state licensure requirements. Legitimate pharmacies that carry the VIPPS seal are listed at www.vipps.info .

Reference:

FDA News Release, US FDA 17 June 2010. (*www.fda.gov*).

Workshop on Pharmaceutical Development of Paediatric Formulations

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

A training workshop on pharmaceutical development focusing on paediatric formulations was organized by the Prequalification of Medicines Programme (PQP) of the World Health Organization (WHO) in Beijing from 21 to 24 June 2010, with the cooperation of the International Pharmaceutical Federation (FIP) and the National Institute for Control of Pharmaceutical and Biological products (NICPBP), (a division of the State Food and Drug Administration (SFDA)) of the People's Republic of China.

This was the fourth workshop on this topic arranged by WHO PQP. The first workshop was held in Cape Town (South Africa), the second in Mumbai (India), and the third in Tallinn (Estonia).

Fifty participants representing national medicines regulatory authorities and the pharmaceutical industry attended the workshop. The primary target participant group was representatives of local manufacturers in China (30 people). Ten SFDA staff and 10 representatives of industry and the medicines regulatory authorities of Indonesia, Hong Kong, South Korea, Thailand and Vietnam also attended the workshop.

The training workshop provided a forum for exchanging and sharing information, knowledge and good practice in developing, formulating and manufacturing medicines for paediatric use. The instructional programme covered topics ranging from elementary physiology and paediatric pharmacokinetics and toxicology, preformulation studies and excipient properties and selection, to manufacturing, scale-up, quality, regulatory and product performance (bioavailability) and stability issues. The course content focused on oral solid (including powders, granules/pellets, tablets and capsules) and oral liquid dosage forms (including solutions and suspensions), with emphasis on how to apply the information and data in the working environment. Participants were given the opportunity to solve paediatric medicine case studies, including group discussion and feedback.

The participants were also introduced to the WHO Procedure for Prequalification of Medicines. A panel was available to discuss questions and to provide answers.

The presenters were from a variety of backgrounds and had a wide range of expertise, including in ethics and clinical trials, pharmaceutical development, quality by design, stability, pharmacokinetics and pharmacodynamics.

Four representatives from manufacturers in China each made a presentation on their practical experience in pharmaceutical development.

Topics covered by the workshop included:

- the need for paediatric medicines: a WHO perspective
- essential medicines and paediatric dosage forms
- from neonates to adolescents:
  - developmental physiology
  - paediatric pharmacokinetics and pharmacodynamics, toxicology

- biopharmaceutical Classification System (BCS)
- ethical considerations in clinical trials
- bioavailability and bioequivalence studies in paediatrics
- pharmacovigilance and safety of medicines in children
- dosage form design and manufacture (tablets, capsules, syrups, etc.)
- scientific principles: excipients, colorants, flavours, and active pharmaceutical ingredient properties
- selection of packaging materials
- practical problems in developing fixed-dose combinations and bi-layer tablets
- suitable paediatric dosage forms
- introduction to development pharmaceutics:
  - laboratory batches, pilot batches, full-scale batches
  - definitions and purpose
  - scale-up issues
  - packaging
- setting acceptance criteria for manufacturing process validation
- industry perspective on practical approaches and experiences in development pharmaceutics
- selecting and developing an appropriate paediatric dosage form using a Quality by Design approach
- stability testing of active pharmaceutical ingredients and finished pharmaceutical products (FPPs)
- analytical method development
- originator and multisource generic FPPs
- specifications
- stability
- parallel development of analytical methods for cleaning validation
- introduction to the WHO Prequalification of Medicines Programme
- applications for prequalification: dossier requirements
  - multisource (generic) products
  - products from ICH regions
  - new products that are not considered as "Innovators" or "Generics"
- inspections in Prequalification (including Good Manufacturing Practice and Good Clinical Practice).
- dossier maintenance (including variations).

Presentations were made in English with simultaneous translation into Chinese. Certificates of Attendance were issued. The course was evaluated by 35 of the participants. (Not all of them answered all the questions in the evaluation form.)

Job-related	Strongly agree	Agree	Disagree	No comment
1. The course helped me develop skills that are important to me.	25	10		
2. The course met my needs.	14	20		
The trainers	Strongly agree	Agree	Disagree	No comment
1. The trainers managed the workshop well.	26	8		
2. The trainers presented the subject matter clearly and accurately.	21	13	1	
3. The trainers handled questions well.	24	11		
Course design	Strongly agree	Agree	Disagree	No comment
1. The course material was clear and well presented.	16	15	3	
2. The presentation materials used were useful.	18	17		
3. The practical work supported the presentation.	17	18		
4. The course duration was correct.	17	18		
5. The course covered the relevant subject matter.	13	20		
Satisfaction	Very high	High	Average	Low
1. My overall satisfaction with the course is	22	13		
2. My awareness of the subject matter PRIOR to the course was	2	5	20	6
3. My awareness of the subject matter AFTER the course is	8	23	4	
Facilities and administration	Strongly agree	Agree	Disagree	No comment
1. The course area was conducive to learning.	21	14		
2. There were sufficient breaks.	21	13	1	
3. The arrangements for breaks were adequate.	19	15	1	
4. I was given clear joining instructions.	21	14		
Overall	Strongly agree	Agree	Disagree	No comment
I enjoyed the course	25	10		
I would recommend the course to others	25	10		

Overall, the feedback was overwhelmingly positive, with the majority of the participants allocating the highest and second highest ranking of "agreement" to the evaluation.
Suggestion for reformulation;
Overall, the feedback was overwhelmingly positive, with the majority of the participants giving a high score for most aspects of the course.

With thanks to all participants, presenters and organizers.

HSA hosts the First Pharmacovigilance Training for ASEAN Countries

Dr Choong Chih Tzer, Senior Regulatory Specialist, Health Sciences Authority, Singapore

Overview

The inaugural WHO-UMC-HSA Basic Pharmacovigilance Training was conducted in Singapore from 31 May to 4 June 2010. This event was the first collaborative initiative by the World Health Organisation (WHO), WHO's Collaborating Centre for International Drug Monitoring, the Uppsala Monitoring Centre (UMC) and Singapore's Health Sciences Authority (HSA). Over 40 participants from nine Association of Southeast Asian Nations (ASEAN) countries (Brunei, Cambodia, Indonesia, Laos, Malaysia, Philippines, Thailand, Vietnam and Singapore) attended the 5-day training conducted in Singapore.

The objective of the training was to equip the participants from the various ASEAN countries with the necessary skills to strengthen their pharmacovigilance capabilities, especially for developing countries that are in their initial stages of establishing their national pharmacovigilance centres. This was well-aligned with the WHO-UMC's continuous drive to communicate the importance of drug safety and pharmacovigilance among countries.

International and Local Panel of Speakers

Internationally renowned experts in the field of pharmacovigilance chaired the event's various training sessions. This panel of international experts comprised of Dr Shanthi Pal, Acting Programme Manager, Pharmacovigilance, WHO; Mr Sten Olsson, Chief WHO Programme Officer, UMC; Ms Monica Plöen, Safety, Support and Services Manager, UMC, and Dr John McEwen, adjunct Associate Professor in Pharmacy, University of Canberra.

To complement the international panel, local clinical specialists were also invited to share their knowledge and expertise in areas of drug hypersensitivities and drug-induced liver toxicities. These experts include Professor Chng Hiok Hee, a senior consultant in the Department of Rheumatology, Allergy and Immunology at Singapore's Tan Tock Seng Hospital and Professor Chow Wan Cheng, the head of the Department of Gastroenterology and Hepatology at the Singapore General Hospital. In addition to the local experts, HSA representatives who presented at this event were Ms. Chan Cheng Leng, Division Director of Vigilance, Compliance and Enforcement and Ms. Belinda Tan, senior regulatory specialist, Vigilance Branch.

Key Topics Covered

Participants familiarised themselves with a balance of both theories and best practices in the area of pharmacovigilance. Topics covered included the concepts of pharmacovigilance, the management of adverse drug reaction (ADR) reporting, pharmacovigilance communications processes, the role of pharmacovigilance in public health programmes, cohort event monitoring and information management tools used in pharmacovigilance such as VigiFlow, VigiBase and VigiSearch. In customizing the course for the participants from this geographical region, topics of local interest, such as the safety monitoring of traditional medicines were included in the programme. Furthermore, active group discussions took place during the causality assessments of ADR reports and the brainstorming on ways to further encourage ADR reporting.

At the closing of the event, the participants from the respective countries formulated and shared their pharmacovigilance plans for the next year. Many participants were committed to further increase the awareness of ADR reporting in their countries.

Moving Forward

Based on the responses received from the participants, this inaugural WHO-UMC-HSA pharmacovigilance training was a success. Participants indicated that the course was of great value to them, with all participants rating the course as a good platform for the development of pharmacovigilance knowledge.

As shared by Dr. John Lim, Chief Executive Officer of HSA, the next step forward would be for countries to apply the knowledge gained in the course to enhance pharmacovigilance capabilities in their countries. This will hopefully pave the way for deeper future collaborations in the area of pharmacovigilance among ASEAN nations to enhance drug safety in the region.

Seventh Meeting of the WHO Advisory Committee on Safety of Medicinal Products

Geneva, Switzerland
26 - 28 April 2010

The WHO Advisory Committee on Safety of Medicinal Products (ACSoMP) has been constituted to provide advice on pharmacovigilance (PV) policy and issues related to the safety and effectiveness of medicinal products. Following is a summary of discussions and recommendations from the Seventh Meeting of the Committee.

WHO strategy for promoting best practices in pharmacovigilance

Any pharmacovigilance (PV) strategy should be aligned with the Millennium Development Goals (1). It should be both health systems and primary healthcare based, focusing on priority medicines in areas where they are most needed. The strategy, currently under development, aims for best practices in PV, through activities that involve the WHO, its Collaborating Centres, the ACSoMP members, national PV centres, health professionals and professional organizations, academia, the public, industry, civil societies and other national and international experts. The primary focus will be on low and middle income Member States.

The draft WHO PV strategy will be presented at the thirty-third Annual Meeting of National Pharmacovigilance Centres in November 2010, at Accra, Ghana.

Serious AEs in preventive chemotherapy interventions for the control of neglected tropical diseases

An overview of the document entitled "Assuring Safety of Preventive Chemotherapy Interventions for the Control of Neglected Tropical Disease- Rev7" was presented and discussed. When finalized, it will be field-tested at national level. WHO is focusing on five Neglected Tropical Diseases (NTDs) for large-scale interventions; Lymphatic filariasis; Onchocerciasis; Schistosomiasis; Soil-transmitted Helminthiasis; Trachoma. Six medicines are prioritized for the large-scale interventions albendazole, azithromycin, diethylcarbamazine, ivermectin, mebendazole, & praziquantel. The document aims to help NTD programme managers to address specific questions related to adverse events (AEs) and to establish a safety surveillance system. An inadequate management of serious adverse events (SAEs) may lead to damage of public health programmes.

[1] http://www.who.int/medicines/mdg/en/index.html

Leveraging collaborations with Global Health Initiatives for building minimum standards for Pharmacovigilance in countries

The Global Fund to fight AIDS, Tuberculosis and Malaria (GF) is an independent public-private partnership that aims to raise and disburse substantial new funds for these three high burden diseases. Principal recipients of these funds are the ministers of health of countries. This financing institution collaborates with the technical programmes within WHO. In October 2002, the GF board made a decision to strongly recommend recipients to implement pharmacovigilance, however the implementation by countries has been lacking. To address this gap, WHO technical guidance is sought to develop the GF PV strategy.

2 parallel work-streams have been identified
a. in immediate term, stimulate inclusion of PV in GF proposal submissions, and
b. in the medium and long term – identify and field test effective PV processes and tools.

Minimum PV requirements and tool kit for Resource Limited Settings (RLS)

A consultation meeting was held in January 2010 to determine the minimum functional standards for PV systems for resource limited countries[2]. The minimum requirements include a national PV centre with designated staff, with clear mandates, a national spontaneous reporting system, a national database (or a system for collating and managing adverse drug reaction (ADR) reports), a national PV advisory committee, and a clear communication strategy for routine information exchange or for communication in crises. A 'PV Toolkit' is defined as a set of practical tools to facilitate country PV processes. The user-friendly kit will carry standard operating procedures (SOPs), generic templates and forms for PV and will guide and assist countries in RLS, to set up and operate PV systems, and to assist in proposal submissions to donors. The toolkit is being developed by a PV consultant; Committee members will help populate this PV tool kit with SOPs and other PV resources.

The toolkit will be presented at a Stakeholders meeting in August or September 2010, followed by its field testing in some 10 to 20 Phase 1 countries.

Procedures for reviewing safety concerns by ACSoMP

Proposed procedures for the review of safety concerns were presented. There is a need to develop a committee governance manual to reflect the current activities. The benefits for this include standardization of process, institutional memory, legacy and an audit trail (a chronological database of activity, output and outcome) of action points taken by the committee. A manual outline was proposed reflecting procedures such as organization of committee, duties and responsibilities of members, relationship with media and industry and conflict of interest. The WHO secretariat was tasked to develop a technical paper on the kind of issues that the committee could address, and the committee process for dealing with the same.

A writing group will draft the broad governance principles, to be reviewed in November 2010 at the Annual Meeting of National PV Centres in Accra, Ghana.

[2] www.who.int/medicines/areas/quality_safety/safety_efficacy/PV_Minimum_Requirements_2010_2.pdf

Guidelines on presenting evidence of safety in applications to the WHO Essential Medicines List (EML)

At the last ACSoMP in March 2009, the first draft of the new guideline on procedures to assess safety aspects in EML applications raised two observations: first, procedures were too demanding for applications for new drugs, in particular if effectiveness-driven, and second, comparative risk and risk assessment of new vs. old drugs should be more structured. At the EML Committee meeting in March 2009, it was recommended that a short version of the extensive proposed guideline be produced, as a substitute of the 4-bullet-point section 11 of the current comprehensive EML guideline for applicants.

The new short bullet point version (largely an abstract of the long version) provides guidance on how to present safety claims supporting any application, various comparators and their justification, different studies and data, demographics of investigated patients with their risk factors, administration of candidate drugs, ADRs and risk.

The bullet point version will be posted on the WHO website along with the long explanatory version by the beginning of November 2010 for consultation and comments.

Access to Signals and Data

Four different data sets had been considered for access outside the WHO Programme: summary statistics; limited database excerpt; complete database extract; and signals. Issues on whether data should be made available free of charge or for a nominal fee were discussed; a caveat and interpretation guidance on how to use these documents will be helpful in preventing misuse and misunderstandings.

WHO will continue to publish Signals in the WHO Pharmaceuticals Newsletter. National Pharmacovigilance Centres will have first access to the Signals, prior to publishing. A working group will prepare a position paper, on data access; the paper will draw upon the 1991 WHA resolution on exchange of information among Member States and the ICDRA resolutions on public access to data.

Strategic (PV) methodological choices and innovations to address current needs and priorities in disease control programmes

The characteristics and value of Spontaneous reporting, Cohort Event Monitoring (CEM), targeted spontaneous reporting, Pregnancy registers, Patient records and Observational studies were discussed. The practical Pharmacovigilance challenge is to consider relevant methods that support a prescriber in making therapeutic decisions. Pharmacovigilance tools are present. However, these need to be integrated to address the needs of policy makers and clinicians. This is a complex topic which will need committee guidelines on tools and interpretation of results.

Data management tools: Paniflow and CemFlow

PaniFlow was originally built with Swissmedic collaboration for managing AE data related to Avian flu H5N1, but was later also taken up by WHO for the H1N1. The tool has built in 'search and statistics' functions. Proposed next steps will be to integrate

Swissmedic and international PaniFlow versions and finalize ongoing translations, evaluate the system and make appropriate updates.

In CEM, a group of patients are monitored while treated with a specific medicine or group of medicines. *CemFlow* is the data management tool for CEM. All events in a control period before and during treatment are recorded. CEM terminology has been developed to collect and code these events. This tool is considerably versatile because of the potential for automated search and stratification. The next steps include pregnancy data entry, export tool to Excel format, extraction of ICSRs on E2B format as well as providing technological solutions for countries with poor internet connectivity.

Guidelines for consumer reporting of adverse drug reactions and adverse events due to medicines

The Committee reviewed a draft guideline for setting up a consumer reporting system. Various suggestions were made, to replace 'consumer reporting' in the title: Public reporting; reporting by medicine users; etc. The Committee discussed content issues: additional information that could be requested (eg, source of medicines, unexpected benefits), barriers to reporting, reporting methods (by telephone, Internet, phone/text messages); seriousness of AEs; central versus de-central reporting systems; how to stimulate reporting; data processing and data management (identification of duplicate reports; coding, storage and analysis of reports); interactions with other parties (industry, media, professional organizations, medicines regulatory agencies and others)

The Committee will review the document further and provide comments to the lead person of the relevant work package in the Medicines Monitoring Project (http://www.monitoringmedicines.org/)

Review of safety of specific medicines: amodiaquine - artesunate

A review of AE reports from Africa involving amodiaquine, artesunate or the combination as suspected drug in the WHO/UMC concludes that there is little evidence of ongoing major problems in Africa with the combination product. However, it is not known whether there are reactions not being reported or if reports are being submitted with delay to the UMC. There are reports implicating combination products in children but those implicating amodiaquine alone and artesunate alone still have to be analysed. Many reports seem to demonstrate typical extrapyramidal reactions and movement disorders. There may be pharmacogenetic reasons and new information has been published about drug-drug interactions with amodiaquine. There is an observed strong correlation of movement disorder AEs with these products in the reports to UMC. But current SPCs do not mention observed side effects like dystonia and extrapyramidal reactions and how health-care professionals should manage them when they occur.

A recent survey of antimalarial drugs undertaken by the United States Pharmacopoeia reported sizeable rates of failure in tests of quality of antimalarial drugs in three African countries. A global review of various investigations being undertaken or available literature would be useful. The WHO secretariat will convene a meeting with various stakeholders, including industry, to review current scientific evidence and assess next steps.

Collaborations with other WHO Programmes

WHO Vaccines programme
A global network for post-marketing surveillance (PMS) of newly pre-qualified vaccines aims to support PMS of newly prequalified vaccines with a standardized approach in adverse events (AE) reports submissions, tools development and assessments. With the Uppsala Monitoring Centre (UMC) playing a pivotal role, 12 member countries are currently involved in this project, with the latest member being China. The expected output is an improvement of reporting, causality assessment, and data analysis at the global level using tools developed at the UMC. In a group meeting held earlier in 2009, a core set of minimum data for collecting AEFI and denominator data were proposed. Vaccine specific modifications have been made to fields within UMC database that were previously missing.

Pandemic H1N1 vaccine safety
There are more than 30 pandemic vaccines licensed globally and over 350 M doses distributed with over 300 M doses administered to date. Due to the pandemic situation, with only one identified antigen, there was an underestimation of product variability and diverse preparations, variation of use and safety profiles. Active surveillance for adverse events following immunization (AEFI) with accurate utilization figures may be of value to the programme. The AEFI reports from countries who received WHO donated vaccines are not proportional as expected. Officially, reporting serious AEFI has been made a precondition to receiving donations.
PaniFlow, the AEFI data management tool during the pandemic, was made available to 95 countries but only 9 countries have expressed interest. There was hesitation to embrace a new software. In part, there was wrong perception that this software was to provide a one time data entry system rather than capacity building for data management.

HIV/AIDS programme – PV for antiretroviral medicines (ARVs)
The ARV Pharmacovigilance Project is being implemented by WHO in collaboration with the UMC. The Project has four key components: 1) development of common tools and definitions; 2) national capacity building; 3) research agenda; and 4) coordination. The common tools and definitions developed include practical handbook on PV, coded definitions, reporting tools, peer reviewed clinical management guidelines, and ARV PV training modules. Some of the new research agenda are studies on d4T toxicity, the safety of NNRTIs in women of childbearing age, tenofovir safety in patient with unmonitored renal status and follow up among patients, like pregnant women, in resource limited settings. Constructive engagement with Pharma industry, assisting countries with treatment guidelines, and helping them meet GFATM requirements with inclusion of PV systems for round 10 proposal submissions are points for immediate and future considerations.

Tuberculosis and key features relating to PV
Some of the drugs used in the treatment of TB are associated with very severe ADRs. These ADRs affect adherence to treatment. Two aspects of the TB control which are making PV more relevant today are scale up in the use of drugs for patients with drug-resistant TB and/or with HIV associated TB. The likelihood of drug toxicity from such regimens is increased. As yet there is no specific mention of PV in the Stop TB Strategy and no WHO handbook dedicated to PV in TB programmes. The immediate work plan includes literature review, collaborative work with UMC for analysis of TB drug database, developing interim advice on Global Fund application, creating a handbook on PV for TB by September 2010, and briefing WHO representatives.

Chagas disease
WHO established a procurement and global distribution system for nifurtimox and benznidazole in 2009 and there is a need for PV to assure the safety of these medicines. WHO has initiated a project to collate and review all available information, to characterize adverse effects associated with nifurtimox and benznidazole. An algorithm was established with well-defined inclusion and exclusion criteria to search and select scientific publications on Chagas disease treatment; to conduct literature review on adverse effects associated with nifurtimox and benznidazole in the treatment of Chagas disease; to summarize available information as a review paper in an indexed journal. Key findings will be presented at the Annual Meeting of National PV Centres in November 2010.

Traditional Medicines
The International Regulatory Cooperation for Herbal Medicines (IRCH) meeting is held annually with working groups tasked to address various issues, including, vigilance of herbal medicines adulteration of products, quality of herbal materials and products, evidence for health based claims, consumer and practitioner awareness and education. Maintaining monographs, regulatory information database and meetings are the main activities. A WHO technical review document on clinical studies on traditional medicines is being developed. Identified top priority area of regulatory concern is the interaction of herbal medicines with other medicines for which a proposed new WHO technical document is in progress. Collaboration should be strengthened between PV programme at WHO HQ, UMC and the new traditional medicine programme on the vigilance of herbal medicines, with a view to information sharing, planning, and to avoid duplication of work

WHO Family of International Classifications
WHO Family of International Classifications includes the International Classification of Diseases (ICD), International Classification of Functioning, Disability and Health (ICF) and International Classification of Health Interventions (ICHI); the International Classification of Traditional Medicine (ICTM) is being developed. The collaboration at the international level includes linking with a global norms and standards development activity, ensuring equal access to global public goods and developing a linguistic platform for adequate representation of Traditional Medicines concepts in different cultures and languages. Historically some work has been done. In the WPRO region, the WHO international standard terminology of traditional medicines (IST) was initiated about 4 years ago.

Updates

Developing a set of indicators for pharmacovigilance
Indicators are broadly classified into 4 groups: indicators on background information in the country, structural indicators, process indicators and outcome/impact indicators. 'Candidate indicators' within these groups have been classified as core, complementary and optional indicators following consultations with national centres, PV experts, and ACSoMP members. With this set of indicators, robust performance evaluation & comparison of level of maturity and self-improvement of centres will be possible.

CEM in Nigeria
CEM was piloted in six geopolitical zones, as a method to capture and characterize the safety profile of ACTs, mainly artemether-lumefantrine and artesunate amodiaquine. The main adverse events (AEs) (body weakness and dizziness, loss of appetite, vomiting and abdominal pain) were similar to ADR profile of ACTs reported in literature. Severe AEs were not common. Patients treated with artesunate- amodiaquine had more AEs but had better treatment outcomes. An important observation was that physicians were splitting the dose of artesunate amodiaquine; all data elements were not always reported, leading to poor quality data; The future plan is to complete data analysis, enter data into CemFlow and scale up to reach 10,000 patients in the cohort.

On the question of ethical clearance, it was noted that, like spontaneous reporting, CEM is part of the routine PV monitoring of patients for adverse events and reactions and should therefore require no special ethical clearance. The Committee will develop a guidance paper about obtaining ethical clearance in CEM as well as a clear guidance on the combined use of CEM and spontaneous reporting.

Medicines Monitoring project (FP7)
This is a EC-funded project with 11 partners/beneficiaries and managed by UMC and WHO. This project will run for 3.5 years with a budget of (approximately) 2 million Euros. The project officially started on 1 Sept 2009.

A kick-off meeting was held for the partner beneficiaries in March 2010 in Uppsala. There are a number of work packages within the project: supporting ADR reporting by consumers; identifying problems related to irrational use of medicines and medication errors; broader use of pharmacovigilance data; developing new methods and tools to support safety monitoring of medicines; and develop learning tools and information database to support healthcare workers in the management of AEs in HIV/AIDS patients.

A data mining method for detecting drug dependence and the CemFlow version 2.0 are two of the project deliverables that have been completed to date. More information can be found on the project website www.monitoringmedicines.org

HOT TOPICS

The Committee agreed that the purpose of a session on hot topics is a good tradition to uphold and part of ACSoMP procedures, adding value to discussions and debates, and form part of developing the PV toolkit to address these issues. Many of these topics are of regulatory concern, and often involve discussions of complex signals, problems of benefit risk assessment, and of public and political concerns. At the seventh meeting, there were 4 broad items under this session: Medicines of current interest, role of PV in identifying counterfeit products, PV in Africa, PV in India.

Medicines of current interest: Typically, the Committee should select the topics from current issues and provide advice proactively, for example, regarding EML, drugs with important /serious AE, of public health consequence. The topics should be relevant to WHO's work, or topics referred from countries. But the role of the Committee will be to provide a summary of its evaluation of evidence, not a recommendation.
The WHO secretariat will develop a guidance document for national centres, on procedures for initiating requests to ACSoMP.

Strategies for combating counterfeit medicines and illicit medicines market: the role of PV: It was argued that in the absence of any other system, PV centres should receive and investigate reports related to counterfeit medicines. A few terms will need to be added in the ADR reporting forms, in order to capture information on counterfeit products. But there will be challenges, for example, the difficulty in ascertaining if the observed lack of effect is due to a counterfeit product or due to a lack of clinical effectiveness.
The Committee agreed that PV tools should be developed with a view to collecting information on poor quality and substandard products.

PV in Africa: Landscape assessment, needs evaluation
An assessment of the true state of PV within Africa was conducted through a questionnaire survey with subsequent telephone interviews. The results reveal that very few PV systems exist and that they are not strong. The common need appears to be related to training, with a specific request for help with either establishing or re-starting a dormant PV programme. There is a need for targeted intervention by the newly established UMC-Africa and the WHO Collaborating Centre for Advocacy and Training in PV, based at the University of Ghana Medical School. The West Africa Health Organization (WAHO) is initiating a PV agenda with 17 countries. One focus of this initiative is using PV systems to combat counterfeits.
ACSoMP will communicate the results of this landscape assessment and the needs of Africa to the Global Fund with the objective of exploring further collaborations.

Pharmacovigilance in India
A brief history of the Indian PV system was presented. India joined the WHO-ADR monitoring programme in 1997 and the National PV programme was established through World Bank (WB) funding in 2004. In 2010, a new structure from the Ministry of Health and Family Welfare and Central Drugs Standards Control Organisation has led to the formation of several peripheral PV centers with reporting structures, with the involvement of academic institutions and formation of 3 panels: signal review; core training; and quality review panels. There will also be an ADR watch-list, based on the the following criteria: monitoring restrictions and withdrawals elsewhere in the world; AEs published in WHO Newsletter; diseases of public health importance; monitoring epidemics/pandemics; signals generated from spontaneous reports; and reports from the media.

Publication of Swissmedic's Final Report on the pharmacovigilance of pandemic influenza (H1N1) 2009 vaccines

Switzerland. Swissmedic (the Swiss Agency for Therapeutic Products) has published its Final Report on the surveillance of adverse events following vaccination against pandemic influenza (H1N1) 2009, based on case reports registered in PaniFlow®. PaniFlow® is the Agency's web-based spontaneous reporting system that was made available online from 1 October 2009 to 31 March 2010. Doctors and pharmacists were asked to report suspected adverse events following immunization (AEFI) against pandemic influenza (H1N1) 2009, by registering the information directly online in PaniFlow®. The monitoring of AEFI reports involved the three Pandemic influenza (H1N1) 2009 vaccines licensed in Switzerland: Celtura®, Focetria® and Pandemrix®.

Up to and including 31 March 2010, Swissmedic received 557 case reports which consisted of 1566 adverse reactions (2.8 reactions per report). Of the 557 reports, 469 were associated with Pandemrix®, 58 with Focetria®, and 30 with Celtura®. Based on the 1.3 million estimated administered doses, the overall reporting rate of adverse events to Swissmedic was 43 per 100 000 doses. There have been 13 reports of syncope and 65 reports of allergic reactions of varying severity soon after vaccination. The Agency states that these reports highlighted the general importance of obtaining a full vaccination and allergy history prior to administering a vaccination, advising and monitoring patients for immediate reactions and being prepared to provide immediate and appropriate medical management should a reaction occur. The final report also describes an analysis of selected adverse events: reports in children, pregnant women, intrauterine fetal deaths, convulsions, deaths, Guillain-Barré Syndrome, herpes zoster, immediate type hypersensitivity reactions, inflammatory arthritis or vasculitis, multiple sclerosis, myalgia, neuropathy, severe skin reactions, uveitis, and vaccine failure.

Swissmedic states that the value of the online reporting system was well demonstrated with the high number of participating health-care professionals and the timely data. Batch number was well recorded in reports and is an essential component in the pharmacovigilance system. Based on the PaniFlow® database, the common reported adverse reactions following pandemic H1N1 (2009) influenza vaccination have corresponded with those described in clinical trials and with the profile from post-marketing experience with seasonal influenza vaccines. The most common reported events were consistent with the expected adverse events from the product monograph and other countries' experience with the same product.

Reference:
Publication of Swissmedic's Final Report on the pharmacovigilance of pandemic influenza (H1N1) 2009 vaccines, Swissmedic
http://www.swissmedic.ch/marktueberwachung/01315/index.html?lang=en