WHO PHARMACEUTICALS NEWSLETTER

World Health Organization

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

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The WHO Pharmaceuticals Newsletter provides you with the latest safety reports, advice, warnings and other updates from regulatory authorities across the world.

In this edition of the WHO Pharmaceuticals Newsletter, you will also find a summary of discussions and recommendations from the Eighth meeting of the WHO Advisory Committee on Safety of Medicinal Products (ACSoMP).

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:
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Risk of methaemoglobinaemia

USA. The U.S. Food and Drug Administration (US FDA) notified health-care professionals and patients that the US FDA continues to receive reports of methaemoglobinaemia, a serious and potentially fatal adverse effect, associated with benzocaine products both as a spray, used during medical procedures to numb the mucous membranes of the mouth and throat, and benzocaine gels and liquids sold over-the-counter and used to relieve pain from a variety of conditions, such as teething, canker sores, and irritation of the mouth and gums. Methaemoglobinaemia is a rare, but serious condition in which the amount of oxygen carried through the blood stream is greatly reduced. In the most severe cases, methaemoglobinaemia can result in death.

The US FDA explained that methaemoglobinaemia has been reported with all strengths of benzocaine gels and liquids, and cases occurred mainly in children aged two years or younger who were treated with benzocaine gel for teething. The signs and symptoms usually appear within minutes to hours of applying benzocaine and may occur with the first application of benzocaine or after additional use. The development of methaemoglobinaemia after treatment with benzocaine sprays may not be related to the amount applied. In many cases, methaemoglobinaemia was reported following the administration of a single benzocaine spray.

The US FDA recommended that benzocaine products should not be used on children less than two years of age, except under the advice and supervision of a health-care professional. Adult consumers who use benzocaine gels or liquids to relieve pain in the mouth should follow the recommendations in the product label. Consumers should store benzocaine products out of reach of children.

(See WHO Pharmaceuticals Newsletter No.2, 2006 for report on mouth and throat use linked with methaemoglobinaemia in the USA and No.6, 2006 in Canada).

Reports in WHO Global ICSR database, Vigibase:

Benzocaine Topical products: Cutaneous, topical and transdermal

Number of reports: 74 (PT Methaemoglobinaemia)

Reference:
FDA Drug Safety Communication, US FDA, 7 April 2011 (www.fda.gov)

Bisphosphonates

Rare atypical fractures of the femur: a class effect of bisphosphonates

Europe. The European Medicines Agency (EMA) announced that the agency's Committee for Medicinal Products for Human Use (CHMP) has concluded that rare atypical fractures of the femur are a class effect of bisphosphonates. Bisphosphonates include alendronic acid, clodronic acid, etidronic acid, ibandronic acid, neridronic acid, pamidronic acid, risedronic acid, tiludronic acid and zoledronic acid.

The CHMP confirmed that the benefits of bisphosphonates in the treatment and prevention of bone disorders continue to outweigh their risks, but that a warning of the risk of atypical femoral fractures should be added to the prescribing information for all bisphosphonate-containing medicines in the European Union. Such a warning had already been included in the product information for alendronate-containing medicines across Europe, following a review by the CHMP's Pharmacovigilance Working Party in 2008. It will now be extended to the whole bisphosphonate class.

The EMA advised prescribers of bisphosphonate-containing medicines to be aware that atypical fractures of the femur may occur rarely. If an atypical fracture is suspected in one leg, then the other leg should also be examined. Doctors who are prescribing these medicines for osteoporosis should regularly review the need for continued treatment, especially after five or more years of use. The marketing authorisation holders of bisphosphonate-containing medicines have been asked to closely monitor this issue.

(See WHO Pharmaceuticals Newsletters No.1, 2011 for safety measures against osteonecrosis and osteomyelitis of jaw in Japan and UK, and No.1, 2010, No.1, 2008, No.5, 2006 and No.6, 2004 for a review on the risk of osteonecrosis of the jaw in Europe, for alert on musculoskeletal pain in the USA, reports of osteonecrosis of the jaw in Australia, and reports of osteonecrosis of the jaw in the USA, respectively).

Reference:
Press release, EMA, 15 April 2011 (www.ema.europa.eu).

Buflomedil-containing medicines

Recommendation for suspension of oral buflomedil-containing medicines; review of injectable buflomedil continues

Europe. The European Medicines Agency (EMA) recommended that the supply of oral buflomedil-containing medicines be suspended in all European Union (EU) Member States where it is currently authorised. This is an interim recommendation pending the finalisation of the continuing review of the benefits and risks of buflomedil solution for injection. The Agency's Committee for Medicinal Products for Human Use (CHMP) will adopt an opinion at the end of the full review. Buflomedil, a vasoactive agent, is used to treat the symptoms of peripheral arterial occlusive disease (PAOD).

The EMA explained that the review of buflomedil was initiated following the decision of the French regulatory authority in February 2011 to suspend the marketing authorisation.

The CHMP considered all available data on the benefits and risks of oral buflomedil, including the benefit-risk assessment carried out by France, data from clinical studies, post-marketing surveillance and published literature, as well as from poison control centres in the EU. The Committee concluded that measures put in place by regulatory authorities had not been able to prevent serious side effects, especially related to overdose, from occurring. The CHMP also noted that the medicine had only been shown to have a limited benefit for patients, measured in terms of walking distance, and the studies assessed had a number of weaknesses. The Committee was therefore of the opinion that the benefits of buflomedil-containing medicines in the form of tablets or an oral solution do not outweigh their risks, and recommended that the supply of these medicines should be suspended throughout the EU.

The EMA advised that doctors should stop prescribing oral buflomedil and consider alternative treatment options, including managing underlying health problems which can increase the risk of PAOD, such as diabetes and high blood pressure.

(See WHO Pharmaceuticals Newsletter No.2, 2011 for the decision by Afssaps to suspend marketing authorizations of buflomedil containing products).

Reports in WHO Global ICSR database, Vigibase:

Buflomedil

Number of reports: 396 (SOC Cardiovascular Disorders, General, SOC Central & Peripheral Nervous System Disorders, SOC Heart Rate and Rhythm Disorders)

Most reported reactions (number of events):

Hypotension:	*35*
Dizziness:	*42*
Headache:	*35*
Tremor:	*39*
Vertigo:	*36*
Convulsions:	*56*
Tachycardia:	*31*

Reference:
Press release EMA, 20 May 2011 (www.ema.europa.eu).

Celecoxib

Marketing authorisation of celecoxib (Onsenal®) in familial adenomatous polyposis withdrawn

Europe. The EMA has finalised its review of the use of the COX-2 inhibitor celecoxib in the reduction of the number of adenomatous intestinal polyps in familial adenomatous polyposis (FAP) and concluded that existing evidence of safety and efficacy does not support the use of celecoxib in FAP patients. This review follows Pfizer's voluntary withdrawal of the marketing authorisation of cerecoxib (Onsenal®) for FAP. Celecoxib-containing products are currently authorised in the European Union for the treatment of the symptoms of osteoarthritis, rheumatoid arthritis and ankylosing spondylitis. This review was initiated because of concerns that celecoxib may be used off-label in FAP indication following the withdrawal of Onsenal®.

The CHMP looked at the available data on the use of celecoxib in FAP patients and concluded that the benefit of celecoxib in FAP patients had not been sufficiently demonstrated and did not outweigh the increased risk of cardiovascular and gastrointestinal side effects, which would result from high dose and long-term treatment used in FAP patients.

Reports in WHO Global ICSR database, Vigibase:

Celecoxib

Number of reports: 4 (Indication: familial adenomatous polyposis)

Reported reactions (number of events):

Dyspepsia:	*1*
Gastric carcinoma:	*1*
Gastritis:	*1*
Rash:	*1*
Rash erythematous:	*1*

Reference:
Press release, EMA, 20 May 2011 (www.hc-sc.gc.ca).

Dolasetron mesylate

Withdrawal of 20 mg/mL intravenous injection due to potential risk of arrhythmias

Canada. Health Canada and Sanofi-Aventis Canada Inc. informed the withdrawal of dolasetron mesylate (ANZEMET®) intravenous injection as it is no longer indicated to prevent nausea and vomiting in adults undergoing chemotherapy.

New data have shown that intravenous administration of the injectable form of dolasetron mesylate is associated with QTc prolongation, to an extent which may potentially result in serious arrhythmias at the doses recommended for the prevention of nausea and vomiting. Therefore Sanofi-aventis Canada Inc. will be removing the injectable form from the Canadian market as of May 10, 2011.

The injectable form of dolasetron mesylate should no longer be used to prevent nausea and vomiting associated with chemotherapy. However, dolasetron mesylate tablets for oral use may still be used as the risk of developing an abnormal heart rhythm with the oral form of this drug is considered less than that seen with the injectable form.

Caution should be exercised with respect to the administration of dolasetron mesylate tablets in patients with renal impairment, elderly patients and in patients with conditions which increase the risk of arrhythmias, such as underlying heart conditions, existing heart rate or rhythm problems, concomitant use of drugs known to affect ECG, bradycardia, and electrolyte imbalance.

(See WHO Pharmaceuticals Newsletter No.1, 2011 for reports of abnormal heart rhythms in the USA.)

Dolasetron

Number of reports: 153 (SOC Cardiovascular Disorders, General, SOC Heart Rate and Rhythm Disorders, SOC Myo-, Endo-, Pericardial & Valve Disorders), including 98 reports of Dolasetron intravenous injection

Most reported reactions (number of events of all products and that of i.v. injection form in the blacket):

Hypotension:	*39 (33)*
Bradycardia:	*29 (21)*
Cardiac arrest:	*26 (21)*
AV block:	*10 (7)*
Tachycardia:	*20 (11)*
Myocardial infarction:	*8 (4)*

Reference:
Advisories, Warnings and Recalls, Health Canada, 26 April 2011 (www.hc-sc.gc.ca).

Ipilimumab

Risk Evaluation and Mitigation Strategy (REMS) - Severe immune-mediated adverse reactions

USA. The US FDA announced that Bristol-Myers Squibb informed health-care professionals about the risk evaluation and mitigation strategy (REMS), developed in collaboration with the US FDA, that is required to ensure that the benefits of ipilimumab (Yervoy®) outweigh the risks of severe and fatal immune-mediated adverse reactions. The REMS consists of a Communication Plan to inform health-care professionals of the serious risks of ipilimumab, to facilitate early identification of these risks, and an overview of recommended management of patients with moderate or more severe immune-mediated adverse reactions.

Ipilimumab was approved March 2011 with the Prescribing Information including a Boxed Warning stating that use of the product can result in severe and fatal immune-mediated adverse reactions due to T-cell activation and proliferation. These immune-mediated reactions may involve any organ system; however, the most common severe immune-mediated adverse reactions are enterocolitis, hepatitis, dermatitis (including toxic epidermal necrolysis), neuropathy, and endocrinopathy. The majority of these immune-mediated reactions initially manifested during treatment; however, a minority occurred weeks to

months after discontinuation of ipilimumab.

The US FDA advised health-care professionals to read the boxed warning and the accompanying full Prescribing Information for a complete description of these risks and their management and to discuss the risks that may be associated with therapy with patients and their caregivers. Clinicians were advised to permanently discontinue ipilimumab and initiate systemic high dose corticosteroid therapy for identified severe immune-mediated reactions and to assess patients for signs and symptoms of enterocolitis, dermatitis, neuropathy and endocrinopathy and evaluate clinical chemistries including liver function tests and thyroid function tests at baseline and before each dose.

Reference:
FDA Drug Safety Communication, US FDA, 6 April 2011 (www.fda.gov).

Prasugrel

Rare but serious hypersensitivity reactions

UK. The Medicines and Healthcare products Regulatory Agency (MHRA) has advised that health-care professionals should be aware of the risk of rare but serious hypersensitivity reactions including, very rarely, angioedema; some of which occurred in patients with a history of hypersensitivity to clopidogrel when prescribing prasugrel (Efient®). Prasugrel is a thienopyridine, belonging to the same class of medicines as clopidogrel, and acts as an inhibitor of platelet activation and aggregation. Co-administered with aspirin, prasugrel is indicated for the prevention of atherothrombotic events in patients with acute coronary syndrome (i.e. unstable angina, non-ST segment elevation myocardial infarction, or ST segment elevation myocardial infarction) undergoing percutaneous coronary intervention.

As at April 2011, nine cases of hypersensitivity reactions including, very rarely, angioedema have been reported worldwide in association with use of Prasugrel in approximately 727 000 patients. Some cases have occurred in patients with a known history of hypersensitivity to clopidogrel, but others have no history of clopidogrel exposure. At present, the mechanism for these allergic reactions is unclear. The time to onset of symptoms ranged from immediately after treatment to up to 5–10 days later.

Health-care professionals are also advised to monitor for signs in all patients, including those with a previous known history of hypersensitivity reactions to thienopyridines and to inform patients of the potential risk of hypersensitivity reactions, including angioedema when prescribing prasugrel.

References:
Drug Safety Update, May 2011, Volume 4, Issue 10, A1, MHRA (www.mhra.gov.uk).

Rosiglitazone

Risk Evaluation and Mitigation Strategy (REMS) - Risk of cardiovascular events

USA. The US FDA notified health-care professionals and the public of new restrictions to the prescribing and use of rosiglitazone-containing medicines. These medicines to treat type II diabetes are sold under the names Avandia®, Avandamet® (contains rosiglitazone and metformin), and Avandaryl® (contains rosiglitazone and glimepiride). Health-care providers and patients must enroll in a special program in order to prescribe and receive these drugs. The US FDA has modified the REMS for Avandamet and Avandaryl because previously, the REMS consisted of only a Medication Guide. The REMS, which now includes a restricted access and distribution program, applies to all three rosiglitazone products.

(See WHO Pharmaceuticals Newsletter No.2, 2011 for suspension of marketing authorizations in New Zealand, No.6, 2010 for new restrictions due to the risk of cardiovascular events in Canada and No.5, 2010 for suspension of marketing authorizations in Europe, new restrictions in the USA and reports in WHO global ICSR database.)

Reference:
FDA Drug Safety Communication, US FDA, 18 May 2011 (www.fda.gov).

Stavudine

Use only when there are no appropriate alternatives, and for the shortest possible time

UK. The MHRA has advised that stavudine (Zerit®) should only be used when there are no appropriate alternatives, and for the shortest possible time, because of an increased risk of potentially severe adverse effects in patients receiving stavudine compared with alternative HIV treatments. Stavudine is a nucleoside reverse transcriptase inhibitor (NRTI) indicated in combination with other antiretroviral products for the treatment of HIV-1 infection in adults and children.

The MHRA reviewed worldwide safety data (including case reports, clinical studies, and published literature) with stavudine and found that cases of potentially fatal lactic acidosis have been reported, both within the first few months of stavudine treatment and also substantially later. An increased risk of lipoatrophy compared with other NRTIs has also been identified. The incidence and severity of lipoatrophy seems to be cumulative over time, and is often not completely reversible on stopping stavudine. Peripheral neuropathy also occurs frequently, reported in up to 20% of patients treated with stavudine. Patients at particular risk are those with a history of neuropathy, excessive alcohol intake, renal impairment, or patients receiving isoniazid concomitantly.

On the basis of these safety concerns, the MHRA considered that the balance of benefits and risks of stavudine is favourable only in a small and highly selected group of patients. Therefore, the licensed indication for stavudine has been restricted to use only in individuals for whom there are no other appropriate treatment alternatives, and only for the shortest period possible in these individuals.

Health-care professionals are also advised to switch all other patients, including those starting and those continuing stavudine, to appropriate alternative therapy as soon as possible and to frequently assess patients taking stavudine for evidence of mitochondrial toxicity, and discontinue treatment if appropriate, if toxicity occurs.

Reference:
Drug Safety Update, April 2011, Volume 4, Issue 9, A2, MHRA (www.mhra.gov.uk).

Tigecycline

Increased mortality in clinical trials - use only when other antibiotics are unsuitable

UK. The MHRA has advised that tigecycline (Tygacil®) should only be used when other antibiotics are unsuitable, because an analysis of pooled results from clinical trials of tigecycline versus comparator drugs in a range of infections has shown numerically higher mortality rates in patients receiving tigecycline. Tigecycline is a glycylcycline antibiotic approved for the treatment of complicated skin and soft tissue infections and complicated intra-abdominal infections.

The license holder for tigecycline completed a pooled analysis of results from all phase 3 and phase 4 trials in the approved indications (complicated skin and soft tissue infections and complicated intra-abdominal infections). Death occurred in 2.3% (52 of 2 216) patients receiving tigecycline and 1.5% (33 of 2 206) patients receiving comparator drugs.

A larger analysis adding results from trials of tigecycline use in unapproved indications (diabetic foot infections, nosocomial pneumonia, and treatment of resistant pathogens) also showed numerically higher overall mortality rates in patients treated with tigecycline versus those treated with active comparators.

The MHRA explained that the cause of these findings is unknown. The possibility that tigecycline has a poorer efficacy and/or safety profile than the comparator drugs cannot be excluded. Patients who develop superinfections, particularly nosocomial pneumonia, seem to be at particular risk of having a poor outcome, including death.

Health-care professionals are advised that numerically higher mortality rates have been reported in patients treated with tigecycline in clinical studies in approved and unapproved indications, compared with patients treated with other antibacterial agents. Patients who develop superinfections, particularly nosocomial pneumonia, seem to be at particular risk of having a poor outcome. Patients should be closely monitored for the development of superinfections. If medically indicated, they should be switched to alternative antibiotic treatment which has been shown to be efficacious in the treatment of the specific infection.

(See WHO Pharmaceuticals Newsletter No.5, 2010 for Label change due to an increased risk of death in the USA.)

Reference:
Drug Safety Update, April 2011, Volume 4, Issue 9, A1, MHRA (www.mhra.gov.uk).

Drug-induced hyponatraemia

Australia. The Therapeutic Goods Administration (TGA) has reported that diuretics, antidepressants, antiepileptics and antihypertensives appear commonly as suspected causes of adverse reactions in reports to the TGA. Hyponatraemia, defined as serum sodium less than 135 mmol/L, is often caused by drugs, with diuretics, antidepressants and antiepileptics, some of the most commonly implicated medicines.

Between January 2009 and 2011, the TGA received 136 reports of hyponatraemia. Drugs well known to be associated with hyponatraemia appear in many reports. Drugs implicated in reports of hyponatraemia to the TGA are as follows.

Thiazide diuretics:	*47*
Antihypertensives:	
Angiotensin receptor blocker:	*28*
ACE inhibitor:	*23*
Antidepressants:	
Selective serotonin reuptake inhibitor:	*22*
Serotonin–noradrenaline reuptake inhibitor:	*20*
Angiotensin receptor:	*7*
Carbamazepine:	*13*

Similar to reports of hyponatraemia received between May 2005 and October 2008, three drug combinations are suspected in many reports, with the combination of a diuretic with an ACE inhibitor or angiotensin receptor blocker appearing in 41 reports. Just over half of the reports, 56% (76), described patients aged 70 or over and 64% (49) of these involved females. Older age is acknowledged to be a risk factor for hyponatraemia. Commonly reported symptoms with hyponatraemia were confusion, dizziness, dehydration, nausea and vomiting, although a number of reports describe asymptomatic hyponatraemia detected on routine laboratory tests.

Reference:
Medicines Safety Update Vol 2, No 2, April 2011 (www.tga.gov.au).

Immune Globulin Subcutaneous (Human)

Risk of thrombotic events with subcutaneous or inappropriate intravenous use

Canada. Health Canada and CSL Behring Canada, Inc. informed that post-marketing reports indicate an association of serious thrombotic events, including deep venous thrombosis, pulmonary embolism and stroke, with the use of Immune Globulin Subcutaneous (Human) (Vivaglobin®). It is also emphasized that the product should be administered only by the subcutaneous route and that administration by other routes is not authorized and may increase the risk of thrombotic events. Immune Globulin Subcutaneous (Human) is authorized for the treatment of adult and paediatric patients with primary immune deficiency (PID).

Reference:
Advisories, Warnings and Recalls, Health Canada, 11 April 2011 (www.hc-sc.gc.ca).

Lenalidomide

Investigation of risk of second primary malignancies in myeloma

UK. The MHRA warned that the use of lenalidomide (Revlimid®) in patients with newly diagnosed multiple myeloma or other unlicensed indications is not recommended and advised that Health-care professionals should be vigilant to the occurrence of second primary malignancies, and should report such events promptly. Lenalidomide is authorised in combination with dexamethasone for treatment of multiple myeloma in patients who have received at least one previous treatment. Lenalidomide is an immunomodulatory agent similar to thalidomide, which has antineoplastic, antiangiogenic, and antierythropoietic properties.

The MHRA explained that data from three large controlled clinical trials investigating lenalidomide use in patients with newly diagnosed multiple myeloma have recently shown a signal of an apparent excess of second primary malignancies in patients treated with lenalidomide. This treatment population falls outside the currently authorised indication for this drug. In these trials, the malignancies were mainly haematological. On the basis of this observation, a review of the balance of benefits and risks of lenalidomide in its authorised indication is being undertaken in the EU. However, at present, it is not possible to conclude that the risk has been categorically established or that the risk is equally relevant to the licensed indication. Nevertheless, the new data emphasise the importance of adhering to the licensed indication.

The MHRA provides the following advice for health-care professionals:

- At present, there is no recommendation to delay, modify, or restrict the use of lenalidomide for patients treated for the indication authorised in the EU.
- The use of lenalidomide in unlicensed indications is not recommended; health-care professionals should carefully consider the balance of risks and benefits of any off-label use.
- Current trials of lenalidomide as an experimental drug are under periodic safety monitoring, and the investigation of the signal for second primary malignancies does not affect enrolment or participation in these trials.
- Health-care professionals should be vigilant to the occurrence of second primary malignancies, and should report such events promptly.

(See WHO Pharmaceuticals Newsletters No.2, 2011 for the risk of thrombosis and thromboembolism in the UK.)

Reference:
Drug Safety Update, May 2011, Volume 4, Issue 10, A2, MHRA (www.mhra.gov.uk).

Long-Acting Beta-Agonists (LABAs)

Use with coricosteroids under evaluation

USA. The US FDA announced that the US FDA required the manufacturers of LABAs to conduct five randomized, double-blind, controlled clinical trials comparing the addition of LABAs to inhaled corticosteroids versus inhaled corticosteroids alone to further evaluate the safety of Long-Acting Beta-Agonists (LABAs) when used in combination with inhaled corticosteroids for the treatment of asthma. The clinical trials will begin in 2011 and the US FDA expects to receive results in 2017.

(See WHO Pharmaceuticals Newsletter No.4, 2010 for new recommendations included in labelling in the USA.)

Reference:
FDA Drug Safety Communication, US FDA, 15 April 2011 (www.fda.gov).

Natalizumab

Update of health-care professional information about the risk of progressive multifocal leukoencephalopathy

USA. The US FDA has updated the natalizumab (Tysabri®) Prescribing Information to give new information about the size of the risk of progressive multifocal leukoencephalopathy (PML), a rare but serious brain infection, associated with the use of natalizumab for the treatment of multiple sclerosis (MS) and Crohn's disease. The update includes new safety information about patients who have taken other drugs that suppress the immune system, who may be at a higher risk for PML. Natalizumab, in a class of medications called immunomodulators, has been approved by the US FDA for the treatment of relapsing forms of MS since November 2004 and for the treatment of moderate to severely active Crohn's disease since January 2008. The revised label includes a table summarizing rates of PML with natalizumab use according to the number of infusions (how long the drug is taken or duration of exposure), and information on a newly identified PML risk factor.

(See WHO Pharmaceuticals Newsletters No.2, 2010 for updates on the risk of PML and IRIS in the UK and the USA as well as No.1, 2010 for recommendations of new measures to minimize the risk of PML in Europe and No.3, 2010 for updates on the risk of PML in Canada).

References:
FDA Drug Safety Communication, US FDA, 22 April 2011 (www.fda.gov).

Tumor Necrosis Factor (TNF) blockers, azathioprine and/or mercaptopurine

Update on reports of hepatosplenic T-cell lymphoma in adolescents and young adults

USA. The US FDA notified health-care professionals that the US FDA continues to receive reports of Hepatosplenic T-Cell Lymphoma (HSTCL), primarily in adolescents and young adults being treated for Crohn's disease and ulcerative colitis with tumor necrosis factor (TNF) blockers, as well as with azathioprine, and/or mercaptopurine. TNF blockers include infliximab (Remicade®), etanercept (Enbrel®), adalimumab (Humira®), certolizumab pegol (Cimzia®) and golimumab (Simponi®).

The US FDA explained that the majority of cases reported were in patients being treated for Crohn's disease or ulcerative colitis, but also included a patient being treated for psoriasis and two patients being treated for rheumatoid arthritis.

Although most reported cases of HSTCL occurred in patients treated with a combination of medicines known to suppress the immune system, including the TNF blockers, azathioprine, and/or mercaptopurine, there have been cases reported in patients receiving azathioprine or mercaptopurine alone.

The recommendations from the US FDA for health-care professionals include the following:

- Educate patients and caregivers about the signs and symptoms of malignancies such as HSTCL so that they are aware of and can seek evaluation and treatment of any signs or symptoms. These may include splenomegaly, hepatomegaly, abdominal pain, persistent fever, night sweats, and weight loss.
- Monitor for the emergence of malignancies when a patient has been treated with TNF blockers, azathioprine, and/or mercaptopurine.
- Know that people with rheumatoid arthritis, Crohn's disease, ankylosing spondylitis, psoriatic arthritis and plaque psoriasis may be more likely to develop lymphoma than the general U.S. population. Therefore, it may be difficult to measure the added risk of TNF blockers, azathioprine, and/or meracaptopurine. Appropriate thrombotic prophylaxis medication should be considered during lenalidomide treatment, particularly in patients with multiple thrombotic risk factors, after careful assessment of the balance of risks and benefits in individual patients.

(See WHO Pharmaceuticals Newsletter No.5, 2009 for notification on increased risk of lymphoma and other malignancies in the USA and Canada, and reports in the WHO global ICSR database.)

Reference:

FDA Drug Safety Communication, US FDA, 14 April 2011 (www.fda.gov).

Eighth Meeting of the WHO Advisory Committee on Safety of Medicinal Products (ACSoMP)

Geneva, Switzerland
31 March - 1 April 2011

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 Eighth Meeting.

As – AQ: Analysis of ADR reports

The committee agreed that based on the UMC data, there is clearly a 'Signal' associating extrapyramidal reactions with the combination of AS-AQ, most likely due to the amodiaquine. More work is needed to understand the incidence and predisposing factors. The Committee was of the opinion that the regular inclusion of the full details of product, dose, dose frequency and concomitant drugs would permit further analysis, including dose/reaction associations and drug interactions.

The mechanism is currently unknown, and may not be directly related to the dose. There have been some patients on very high doses who have not experienced these reactions.

This 'Signal' is more or less the first from African data. The Committee recommended publishing this Signal and sharing the details with the manufacturer for a possible update of the Summary of Product Characteristics. The committee also suggested that the manufacturer should be contacted, to design a follow up study, to substantiate the present evidence and Signal of extrapyramidal symptoms with As-AQ.

PV Toolkit

The Pharmacovigilance Toolkit is being developed as a Pharmacovigilance resource repository for low and middle income countries looking to develop a good quality, standard pharmacovigilance system. The WHO Collaborating Centre for Advocacy and Training in Pharmacovigilance, Ghana has been leading the work on the Toolkit, with support from the WHO, UMC and the Global Fund.

A Malaria 'chapter' has been added, funded by the Roll Back Malaria partnership. Discussions are ongoing for developing a HIV chapter and perhaps, a TB chapter within the Toolkit. Multiple partners will be involved in the overall content development.

The Committee recommended that WHO would oversee the development; a technical/governance committee will be drawn from within the ACSoMP, to critically review and approve specific toolkit contents. But the WHO CC / UMC-A in Ghana will retain responsibility for the everyday maintenance of the Toolkit with technical overview from the UMC.

Training activities and PV training modules

A comprehensive pharmacovigilance curriculum is being developed as a collaborative effort between the International Society of Pharmacovigilance (ISoP), WHO and the UMC. There is a small writing group. The course structure will be hierarchical, with different levels, consisting of modules that are compact and defined, and reflect the complete field of pharmacovigilance, to be taught as separately, as individual modules, or as a combination of two or more modules. A set of tasks for practical hands-on training will accompany the teaching modules.

The committee approved the ongoing work on pharmacovigilance curriculum development as timely and of universal value; and recommended that there should be a review process similar to the one for the pharmacovigilance toolkit. A working group made of representatives from the UMC, WHO and ISoP should be established, to outline what should be incorporated into trainings for different focus groups. WHO will coordinate the project, with ACSoMP members invited to review and advice on specific aspects.

CIOMS Activities

Update on the working groups:

- Working Group IX – this is a working group to discuss a harmonised view on risk management and specifically risk minimisation. The goal is to develop a risk minimisation toolkit, similar to the pharmacovigilance toolkit but more as a complement than an overlap.
- Working Group X – this is a new working group, to focus on systematic reviews and meta-analysis as good practices in regulatory medicine. The goal is not to produce guidelines but to discuss the interpretation of meta-analysis and develop a consensus on scientific and methodological criteria that represent good practices. These criteria would be used by both industry and regulators.
- CIOMS-WHO joint working group on vaccine pharmacovigilance: the group has been working on a draft report which is now being reviewed by the members. A close relationship has been maintained with the Brighton Collaboration with the purpose of disseminating the case definitions by the Brighton Collaboration. The draft report proposes some standardized definitions for the monitoring of safety of vaccines. The goal is to publish the report this year, through the WHO publication system.

Caveat document for SIGNAL and other data from Vigibase

When requested, the UMC provides data from the WHO global individual case safety reports (ICSR), database (Vigibase) along with a Caveat document, to make sure that the recipient will have a basic idea of what needs to be considered when reviewing the data. The document has not been updated since 1992, when it was first compiled. The UMC has now revised the Caveat document which was then approved by the Committee.

Making some Vigibase data publicly available: a concrete proposal

The Committee discussed issues around increasing public access to the data in Vigibase. This would need to be done in a responsible, stepwise fashion. Some extensions will be made to the current data retrieval interface being used by national centres, a new search tool. Those who are not members of the national centres will be able to log on but with a different level of access, for example, to some summary tables. The UMC is preparing to make these summaries available and the necessary search tool. The data presentation will be modelled on that used by the MHRA in the UK. A dry run will be carried out with all national centres, to test their reaction to the search tool and summary tables.

ACSoMP agreed that increasing public access to the data will raise overall awareness, to the importance of the work carried out by the UMC and would also give access to a valuable source of information.

Antibiotic resistance - pointers from pharmacovigilance data

One of the work packages within the Monitoring Medicines project (http://monitoringmedicines.org/) involves methodological development in investigating reports of therapeutic ineffectiveness. It may be possible to use this methodology to identify cases of antimicrobial resistance within the data base. The UMC had invited representatives from STRAMA (The Swedish Strategic Programme Against Antibiotic Resistance) and ReAct (Action on Antibiotic Resistance) to a meeting to discuss possible areas of collaboration. Using the global database and the methodology developed within the Monitoring Medicines project, the UMC has identified a list of possible cases of antibiotic resistance, but this needs to verified on a national level to ensure that the right signals are being detected.

Health professionals should be encouraged to submit cases of suspected resistance to their local pharmacovigilance centre. The Committee suggested developing a policy on reporting recommendations for national centres, to submit cases of lack of therapeutic effectiveness, particularly in relation to antimicrobials.

Creating a quorum for publishing in pharmacovigilance

There are very few pharmacovigilance papers coming from national centres, especially from developing countries. ACSoMP proposes that technical support and assistance are provided to increase the number of publications. The first endpoint of this is to increase the strategic visibility of pharmacovigilance as well as its advocacy. The second endpoint is to improve the sharing of pharmacovigilance information to a wider community, as a form of outreach service. A reviewer group will be formed consisting of senior experts and scientists in pharmacovigilance, who are willing to providing assistance on a voluntary basis. National centres will be notified upon the creation of the reviewer's group and its purpose.

The Vaccines Blueprint Project

There are 71 developing countries where AEFI monitoring is not implemented. In many of these countries, there is no AEFI monitoring at all, meaning that many vaccines are used with little to no feedback regarding vaccine reactions. There is huge variation in the way vaccine reactions are detected in the world.

The purpose of the global vaccine blueprint project is to provide a global support platform for capacity building in low and middle income countries. A concept of minimal capacity at country level that will involve immunization programmes, regulatory authorities and other supporting bodies like national pharmacovigilance centres and national AEFI review committees is being proposed.

The discussions at the meeting of the ACSoMP focused on the model for a global AEFI database. The group concluded that a global vaccine database is needed but this already exists, in Vigibase. However some improvements are needed, to accommodate the uniqueness and specificities of vaccines, with certain data fields included in the reporting format in order to maintain a functional database and for efficient and effective signal detection.

Collaborating Centres and Centres of Excellence for improving outreach and country support in pharmacovigilance

The landscape of pharmacovigilance is changing, donor agencies are promoting better access to medicines. The challenge now is to promote pharmacovigilance. Resources are limited within WHO, thus work needs to be directed more through collaborating and national centres, with the view to developing, sustaining and promoting pharmacovigilance in settings where it is most needed. Strategically, WHO is reaching out to countries through collaborating centres and other centres of excellence in pharmacovigilance. However clear guidelines are needed, in establishing these centres and how to work with them. A working paper will be drafted, to describe the terms of reference for satellite centres. This paper will be shared with the Committee, for review and further advise.

Medicines Patent Pool Initiative

UNITAID established the medicines patent pool in 2009, to improve access to patents and facilitate the development and production of life-saving, more affordable, and more suitable medicines. Many pharmaceutical companies want to be involved as it strengthens their position and image as a leader in improving access to medicines. The initiative will collaborate with the WHO prequalification programme, to ensure that good quality generic medicines are available through this scheme. With regard to responsibilities of safety monitoring, the Committee recommended forming a working group, to include and strengthen pharmacovigilance within the scheme of work of the Medicines Patent Pool.

Chagas disease, HIV/AIDS, TB, Monitoring Medicines Project: updates

Chagas disease

WHO established a procurement and global distribution system for nifurtimox and benznidazole in 2009. Organizations such as MSF are involved in providing treatment in resource limited settings. However, pharmacovigilance systems are not present in these settings. There is a need for PV to assure the safety of these medicines.

The Committee recommended developing a plan to assist the integration of pharmacovigilance into Chagas disease programme. A small working was appointed to follow up this topic.

HIV/AIDS: pharmacovigilance updates

Tanzania Cohort Event Monitoring (CEM) Project – six sentinel sites, all based in Dar Es Salaam, will implement this method for the safety monitoring of medicines in HIV treatment programmes. The aim is for 250 enrolments per month of patients starting treatment for the first time, including pregnant women and children. The project is currently being implemented.

WHO partnership for 'targeted spontaneous reporting' with the Academic Model Providing Access to Healthcare (AMPATH) programme in Kenya: the objective is to test a feasible and sustainable method for documenting antiretroviral toxicity in a resource-constrained clinical setting, directly linked to the national pharmacovigilance programme. A subset of 1000 patients will be interviewed about experiences and perceptions of adverse effects.

TB – pharmacovigilance updates

Approximately nine million cases of TB are reported each year, with 1.7 million of these resulting in death, 400,000 of which are HIV associated. These are cases that are demonstrating resistance to the usual drugs.

Not only is there no provision for routine pharmacovigilance reporting, many MDR cases do not get reported either. A 'practical handbook on the pharmacovigilance of antituberculosis medication' is being developed. The current work on updating the Stop TB Strategy needs to include pharmacovigilance. The Committee recommended that this and issues related to pharmacovigilance of TB medicines in Global Fund Grants should be discussed at the next meeting.

Monitoring Medicines Project update

The EC-funded Monitoring Medicines project was developed by WHO and is currently being implemented as a partnership of 11 countries and coordinated by the UMC. The key objectives are to:

- support and strengthen consumer reporting
- expand the role and scope of pharmacovigilance centres (medication errors)
- promote better and broader use of existing pharmacovigilance data (dependence and substandard quality)
- develop additional pharmacovigilance methods to complement spontaneous reporting systems and
- develop a learning tool for the management adverse events with ARVs.

Pharmacovigilance Indicator: Update

A set of core and complementary indicators have been developed. There are three classes of indicators:

- Structural
- Process
- Impact/outcome indicators
- The indicators are being validated.