WHO PHARMACEUTICALS NEWSLETTER

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

The aim of this 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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NEWS & ISSUES

In this issue we bring you the recommendations from the fifth meeting of the Advisory Committee on Safety of Medicinal Products (ACSoMP). Some of the recommendations relate to ongoing projects, such as the patient safety pilot project for expanding the scope of national pharmacovigilance centres; others refer to new initiatives, such as developing indicators for measuring pharmacovigilance capacity and the impact of interventions in countries. Worldwide serious, acute allergic-type reactions have been reported in patients who received contaminated heparin. We have included a brief summary of regulatory actions that followed these events.

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Regulatory Matters

Safety of Medicines

Chlorproguanil / dapsone / artesunate

Further development of 'triple' combination product terminated; 'double' combination product recalled

Worldwide. GlaxoSmithKline (GSK) and Medicines for Malaria Venture (MMV) have decided to terminate the further development of Dacart™, a fixed-dose combination antimalarial product of chlorproguanil, dapsone and artesunate (CDA). GSK has also commenced a product recall process at pharmacy level in Kenya, for LapDap™, another anti-malarial product containing chlorproguanil and dapsone (CD). These decisions are based on data from two Phase III clinical trials assessing the efficacy and safety of CDA (Dacart™) and CD (LapDap™); significant reductions of haemoglobin levels in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency have been observed with both CDA and CD. Chlorproguanil-dapsone (LapDap™) was granted a marketing authorization in July 2003 by the United Kingdom Medicines and Healthcare products Regulatory Agency (MHRA) for the treatment of uncomplicated falciparum malaria. Chlorproguanil-dapsone (CD) was contraindicated in patients with known G6PD deficiency. In view of the potential widespread use of CD (LapDap™) in malaria endemic sub-Saharan Africa, the high prevalence of G6PD deficiency in the region (estimated to affect around 10-25% of the population in sub-Saharan Africa) and the limited availability of screening tests for this genetic condition in Africa, WHO had undertaken a safety assessment of the product in 2004, to provide recommendations on the safe use of CD (LapDap™) in Africa. The WHO expert group cautioned against the use of the medicine in G6PD deficient patients and made the following recommendations:

1. This medicine should be used only if a diagnosis of malaria is confirmed.
2. CD should be used only after severe anaemia (haemoglobin concentration < 5 g/dl) and G6PD deficiency have been excluded by appropriate tests. In patients with a haemoglobin concentration of 7 g/dl, administration of CD should be considered with caution and should be undertaken only under clinical supervision, with monitoring of the haemoglobin concentration. The diagnosis of methaemoglobinaemia is less important.
3. In areas where G6PD deficiency is prevalent but appropriate tests are not available, an alternative antimalarial medicine should be used.
4. If there is no suitable alternative, CD should be used but in cognizance of the haematological risks associated with this medicine.

The group also advised that these recommendations should be reconsidered when more data becomes available from pharmacovigilance and active post-marketing surveillance. The WHO safety assessment report also provided a series of recommendations for ongoing and planned clinical trials as well as phase IV studies to gather the necessary evidence on safety of CD (LapDap™), including in malaria patients with G6PD deficiency. However, several CD (LapDap™) phase IV studies which started in African countries did not continue beyond April 2006 due to low utilization of this medicine. Research on the safety aspects mainly continued as part of the Medicines for Malaria Venture (MMV) - sponsored studies on chlorproguanil-dapsone-artesunate (CDA).

GSK's multi-center, double-blind Phase III clinical trial of chlorproguanil-dapsone-artesunate (CDA) versus the combination antimalarial lumefantrine-artemether (Coartem®) in Africa suggest a strong association between haemolytic anaemia and CDA treatment for uncomplicated falciparum malaria in G6PD deficient patients. The study included 1372 patients. Study results showed a significant reduction in haemoglobin due to haemolytic anaemia in patients with G6PD deficiency, with lowest levels of haemoglobin occurring seven days after treatment. At day seven, 35% of the patients with G6PD deficiency treated with CDA had a reduction in haemoglobin of more than 2g/dl compared to 8% of patients treated with Coartem®, and 10% of the patients with G6PD deficiency treated with CDA had a reduction in haemoglobin of more than 4g/dl compared to 0% of patients treated with Coartem®. 38% of the male patients with G6PD deficiency had severe anaemia after treatment with CDA, compared to 0% in the group treated with Coartem®. In total, 15 patients had severe post-treatment haemolysis requiring blood transfusion in the study: all 15 were in the CDA treated group, 13 of whom were G6PD deficient.

References:

1. Press Release. GlaxoSmithKline and Medicines for Malaria Venture, 29 February 2008, London, UK; Geneva, Switzerland.

2. Review of the safety of chlorproguanil-dapsone in the treatment of uncomplicated falciparum malaria in Africa: Report of a Technical Consultation convened by the World Health Organization. WHO, 2005, Switzerland

(http://www.who.int/malaria/docs/LapDap.pdf).
3. Information Exchange System Alert No. 117. WHO Drug Alerts, 4 March 2008 (www.who.int/medicines).

Deferasirox

Reports of hepatic failure

Canada, USA. Novartis has issued a public communication and a `Dear Health-care Professional' letter, advising of updated safety information regarding reports of hepatic failure with deferasirox (Exjade). According to Novartis, cases of hepatic failure have been reported internationally following post-marketing use of deferasirox; some of the cases had a fatal outcome. Most of the cases involved patients with multiple medical conditions, including multi-organ failure and liver disease (cirrhosis). The deferasirox (Exjade) product monograph has been updated accordingly (although a causal relationship between deferasirox and hepatic failure has not been established). There have been a total of 24 international reports of hepatic failure (21 from postmarketing, three from clinical trials); the estimated total cumulative exposure to deferasirox (Exjade) was 36 797 patients as of 31 October 2007. No patient with normal liver function or without additional life-threatening complications has developed liver failure. The company reminds health-care professionals that liver function should be monitored monthly and that deferasirox should be discontinued if there is unexplained, persistent and progressive liver function deterioration. Novartis says that a post-marketing report of hepatic failure and encephalopathy was reported to the United States Food and Drug Administration (US FDA) by a patient in the US. The patient, who had a history of alcohol use and slightly abnormal liver function, received deferasirox for five days. The patient received deferasirox for a non-approved use while having a serum ferritin level of > 10 times lower than the recommended level for deferasirox initiation. Following discontinuation of deferasirox, the patient recovered. Although the potential role of deferasirox in this case could not be excluded, following a review, Novartis and external medical experts agreed that there were extenuating circumstances in this case.

(Novartis Pharma had also issued a letter about possible association between the use of deferasirox and renal failure and cytopenia that were reported in Canada and in Switzerland; see WHO Pharmaceuticals Newsletter No. 2, 2007.)

Reference:
Reactions weekly (Adis, New Zealand) 1193: 2, 15 March, 2008.

Injectable colchicine

Action against unapproved injectable colchicine

USA. The US FDA intends to take regulatory action against companies marketing unapproved injectable colchicine, a drug used to treat gout. The Agency emphasizes that colchicine is highly toxic and can easily be given in excessive doses, especially when administered intravenously. The US FDA is aware of 50 reports of adverse events associated with *intra venous* colchicine use, including 23 deaths. It says that three of the deaths, which occurred in March and April 2007, were associated with the use of compounded colchicine that was eight times more potent than stated on the label, due to a preparation error. The US FDA explains that, in addition to being manufactured by pharmaceutical companies, injectable colchicine products are sometimes manufactured by compounding pharmacies, often for the treatment of back pain. The Agency notes that it has not approved colchicine in any dosage form for the treatment of back pain.

Reports in the WHO ICSR database:
Colchicine - injectable
Death - 14
(USA, 1991 – 2002).

Reference:
FDA News. US FDA, 6 February 2008 (www.fda.gov).

Ketoconazole

Several indications removed

UK. The prescribing information for ketoconazole (Nizoral) tablets has been updated with the removal of several therapeutic indications because of the risk of serious hepatotoxicity and availability of other effective antifungals. Following a review of risks and benefits, the MHRA advises that oral ketoconazole should only be used for *malassezia* folliculitis, dermatophytosis and chronic candidosis, which cannot be treated topically. Ketoconazole should only be used in patients with infections resistant to fluconazole, terbinafine or itraconazole, or in patients who are intolerant to these drugs. The agency notes that the risk of serious hepatotoxicity increases with duration of oral ketoconazole treatment and that courses of > 10 days should only be given after balancing risks and benefits of continued treatment and full consideration of the extent of treatment response. The MHRA advises health-care professionals that liver function must be monitored prior to ketoconazole initiation, at week two and four of therapy, and continued monthly. If any liver function parameters are higher than three times the

normal limit, ketoconazole should be discontinued.

Reference:
Drug Safety Update, Vol.1(8): 2, March 2008 (www.mhra.gov.uk).

Meprobamate

Benefit / risk profile no longer favourable

UK. The MHRA no longer considers the balance of benefits and risks for meprobamate-containing products to be favourable. Meprobamate is a carbamate used for short-term treatment of anxiety states or musculoskeletal disorders with muscle tyension or painful muscle spasm. The Agency advises that there are risks of dependence, withdrawal, abuse and other unpleasant adverse effects associated with meprobamate; that there are safer alternatives to meprobamate. The MHRA is in discussion with the three UK marketing authorization holders for meprobamate products about a phased withdrawal of these products from the UK market. The Agency is advising health-care professionals that treatment with meprobamate should not be initiated. (Meprobamate is the main active metabolite of carisoprodol; the EMEA has recommended suspending the marketing authorization for all medicinal products containing carisoprodol because the risks from these medicines outweigh their benefits; see WHO Pharmaceuticals Newsletter No. 6, 2007).

Reference:
Drug Safety Update, Vol.1(7): 5, February 2008 (www.mhra.gov.uk).

Modafinil

Risk of psychiatric symptoms; serious skin reactions

UK. The MHRA has advised that modafinil (Provigil) product information has been updated to include the risk of psychiatric symptoms and serious skin reactions. Modafinil is a drug used to treat excessive sleepiness caused by narcolepsy. Stevens Johnson syndrome, toxic epidermal necrolysis and erythema multiforme have been reported in association with modafinil. These reactions have usually occurred within five weeks of treatment, but isolated cases have occurred after > 3 months. Hallucinations, delusion, aggression, suicidal ideation, psychosis and mania have also been reported in association with modafinil. These conditions have mainly occurred in patients with a history of mania, depression or psychosis. The MHRA advises health-care professionals that modafinil should be permanently discontinued at the first sign of rash or psychiatric symptoms. The agency also advises that modafinil should be used with caution in patients with a history of depression, mania, psychosis, or alcohol, drug or illicit substance abuse. (See WHO Pharmaceuticals Newsletter No. 1, 2008 for serious skin reactions reported with modafinil in Canada).

Reports in WHO ICSR database:
Modafinil – 1997 - 2008

Hallucination	30
Depersonalization	14
Personality disorder	10
Paranoid reaction	16
Aggressive reaction	18
Agitation	30
Manic reaction	17
Psychosis	28
Psychosis manic-depressive	5
Epidermal necrolysis	4
Erythema multiforme	4
Stevens Johnson syndrome	9

Reference:
Drug Safety Update, Vol.1(8): 5, March 2008 (www.mhra.gov.uk).

Mycophenolate mofetil and mycophenolic acid

Reports of multifocal leukoencephalopathy

Europe, USA. Mycophenolate mofetil (CellCept) is approved to prevent heart, liver, and kidney transplant rejection and mycophenolic acid (Myfortic) is approved to prevent kidney transplant rejection. Mycophenolate mofetil is metabolized in the body to mycophenolic acid. Both these products are used with other drugs to suppress the immune system. On February 2008 Roche wrote to health-care professionals in Europe about isolated cases of progressive multifocal leukoencephalopathy (PML) that were observed in patients receiving mycophenoplate mofetil (CellCept). Roche wrote that although confounding factors, in particular the underlying disease were associated with these cases of PML, the contributory role of mycophenoplate mofetil could not be excluded. The Summary of Product Characteristics (SPC) for mycophenoplate mofetil has been updated to reflect this information. Later, on March 2008, Roche informed the US FDA about this letter that was issued in Europe. US FDA is reviewing all relevant data, and has also asked Novartis, the maker of mycophenolic acid (Myfortic), for data on PML cases and to revise the mycophenolic acid prescribing information to include the same information about PML as included in the mycophenolate mofetil prescribing information. When completed, the Agency will communicate the conclusions of its review to the public. PML is a rare disorder that affects the central nervous system. It usually occurs in patients with immune systems suppressed by disease or medicines. Signs and symptoms of PML can include localized neurologic signs and symptoms

including vision changes, loss of coordination, clumsiness, memory loss, difficulty speaking or understanding what others say, and weakness in the legs. Many patients who develop PML die and those who survive may have permanent disability due to irreversible nerve damage.

References:

1. 'Dear Health-care Professional' letter, P212828. Roche, 18 February 2008.
2. Communication about an ongoing safety review of CellCept (mycophenolate mofetil) and Myfortic (mycophenolate acid). US FDA, 10 April 2008 (www.fda.gov).

Oseltamivir

Label to include information on neuropsyciatric events

USA. The oseltamivir(Tamiflu) prescribing information has been updated to reflect the US FDA Pediatric Advisory committee recommendations regarding neuropsychiatric events. The label will now include information regarding an association between influenza and neuropsychiatric adverse events and that these reports are uncommon. The label has been revised as follows: Influenza can be associated with a variety of neurologic and behavioral symptoms which can include events such as hallucinations, delirium, and to be uncommon based on oseltamivir (Tamiflu) usage data. These events were reported primarily among pediatric patients and often had an abrupt onset and rapid resolution. The contribution of oseltamivir (Tamiflu) to these events has not been established. Patients with influenza should be closely monitored for signs of abnormal behavior. If neuropsychiatric symptoms occur, the risks and benefits of continuing treatment should be evaluated for each patient.

(Please refer to WHO Pharmaceuticals Newsletter No. 6, 2006 and No. 2, 2007 for previous postings on oseltamivir and neuropsychiatric events.)

WHO adverse reactions database:
Oseltamivir (Tamiflu) - reported 2000 – 2008
Totally 140 reports; main reactions:

Anxiety	11
Nervousness	13
Anorexia	23
Hallucination	23
Insomnia	34
Agitation	14
Confusion	26

Reference:

'Dear Health-care Professional' letter from Roche, February 2008 (www.fda.gov).

peginterferon-α-2a 180µg once weekly. Peripheral neuropathy has been uncommonly reported in patients receiving telbivudine monotherapy. The product information for telbivudine will now include warnings of an increased risk of peripheral neuropathy when telbivudine and peginterferon-α-2a are co-administered. An increased risk cannot be excluded for other interferons-α (pegylated or standard). The EMEA has advised that if peripheral neuropathy is suspected, telbivudine treatment should be reconsidered. Benefits of concomitant therapy with telbivudine and interferon-α have not been established.

Reference:

Media Release. EMEA, 14 February 2008 (www.emea.europa.eu).

Zanamivir

Reports of delirium and abnormal behaviour

USA. The WARNINGS AND PRECAUTIONS sections of the prescribing information for zanamivir (Relenza) has been updated with information from postmarketing reports (mostly from Japan) of delirium and abnormal behaviour leading to injury in patients with influenza who were receiving neuraminidase inhibitors, including zanamivir. These events were reported primarily among pediatric patients and