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EDITORIAL

In addition to the usual updates on recent drug safety and regulatory information for medicines, this issue of the newsletter features an article summarizing the decisions regarding the use of Selective Serotonin Reuptake Inhibitor (SSRI) -antidepressants in children. Most of these products appear to have a negative benefit-risk balance when used in treating major depressive disorder (MDD) in children.

HIV/AIDS was one of the key health issues that figured in the discussions of the recently concluded Fifty-seventh World Health Assembly (WHA) in Geneva. Through Resolution WHA57.14 on HIV/AIDS (http://www.who.int/gb), the WHA requested the Director-General to strengthen the WHO prequalification project managed by the World Health Organization (WHO) for pharmaceutical and diagnostic products to diagnose, treat and manage HIV/AIDS and urged Member States to make best use of WHO's list of prequalified antiretroviral drugs that meet international quality standards (see http://mednet3.who.int/prequal for key facts on the WHO prequalification project).

With the global focus on treating HIV, and consistent with WHO's 3 by 5 initiative to provide treatment to three million HIV patients by the year 2005, it is timely that a training course will be held in September 2004 in South Africa to encourage the integration of pharmacovigilance for antiretrovirals in some sub-Saharan African countries. Details of this course as well as the complete course material will be made available on the website of the Department of Essential Drugs and Medicines Policy (EDM) http://www.who.int/medicines at a later date, after the course.

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Label to indicate risk of hyperglycaemia and diabetes

USA. The United States Food and Drug Administration (US FDA) has requested that Bristol-Myers Squibb Company, the manufacturer of the atypical antipsychotic drug aripiprazole (Abilify) should update the prescribing information for the drug to reflect the risk of hyperglycaemia and diabetes in patients treated with this drug. More recently, Novartis, under advice from the US FDA has also made similar changes to the prescribing information for clozapine (Clozaril) antipsychotic tablets. The US FDA has recommended these revisions after reviewing data related to the use of atypical antipsychotics and hyperglycaemia with its related symptoms (e.g., polydipsia, polyuria, polyphagia and weakness). The FDA has concluded that all atypical antipsychotics should be updated to include information about the potential for these adverse events. Patients with risk factors for diabetes should undergo baseline screening before treatment with any atypical antipsychotic drug and routine monitoring should be undertaken throughout therapy to mitigate the risk of patients developing serious metabolic complications. In January 2004 AstraZeneca Pharmaceuticals LP, manufacturer of atypical antipsychotic agent quetiapine fumarate (Seroquel), had warned health professionals that patients should be monitored for glucose control before starting treatment with atypical antipsychotics. More recently, in April 2004, the company has issued an additional letter that besides pre-treatment monitoring, patients should also be monitored periodically for worsening of glucose control throughout treatment.

References:

1. *'Dear Healthcare Practitioner' letter from Bristol-Myers Squibb Company, 25 March 2004. Available from URL: www.fda.gov/medwatch*
2. *'Dear Healthcare Provider' letter from Novartis, 01 April 2004. Available from URL: http://www.fda.gov/medwatch*
3. *'Dear Healthcare Provider' letter from AstraZeneca Pharmaceuticals LP, 22 April 2004. Available from URL: http://www.fda.gov/medwatch*

MUROMONAB-CD3

Serious adverse reactions in paediatric patients

Canada. Janssen-Ortho Inc., under advice from Health Canada is warning health professionals that muromonab-CD3 (ORTHOCLONE OKT*3) is not approved for paediatric use (age up to 17 years) in Canada. Muromonab-CD3 is a murine monoclonal antibody indicated for the treatment of acute renal, cardiac, and hepatic allograft rejection refractory to conventional anti-rejection therapy or when conventional therapy is contraindicated in adult patients. Paediatric patients treated with this product may be at an increased risk of developing serious neurological complications, most notably cerebral oedema and herniation; nine cases of cerebral oedema have been reported worldwide since 1986, with six deaths due to cerebral herniation. Paediatric patients treated with muromonab-CD3 may also be at increased risk of lymphoproliferative and infectious complications compared to adults. A large proportion of children may not have been infected by pathogens such as herpes viruses prior to transplantation and are therefore more susceptible to developing primary infections from the grafted organ following immunosuppression with muromonab-CD3. Janssen-Ortho Inc. is currently working with Health Canada to update the Canadian Product Monograph to include the above information.

Reference:

Letter to Hospital Chief of Medical Staff, from Janssen-Ortho Inc., 13 May 2004. Available from URL: http://www.hc-sc.gc.ca

NU BAO

Presence of animal derivatives and human tissue poses health risks

UK. The patient information leaflet for a traditional Chinese medicine named Nu Bao lists human placenta, deer antler (*Corna cervi oantotrichum*) and donkey skin (*Colla cori astini*) as the ingredients present in the capsules of the product. Although the information on the source of these ingredients is limited, the Medicines and Healthcare Products Regulatory Agency (MHRA) advices that all animal and human tissue derivatives carry a potential risk of infectious diseases due

to the transmission of infective bacteria and viruses. The MHRA is therefore advising that consumers should not take this product. Current users should stop taking the product and should consult their doctor if they feel unwell. The MHRA has written to suppliers to cease marketing Nu Bao with immediate effect.

Reference:
Herbal Safety News, May 2004. Available from URL: http://medicines.mhra.gov.uk

OTC DRUGS

New labelling rules to increase safety

USA. New US FDA labelling rules for over-the-counter (OTC) drugs will increase safety for patients with certain medical conditions. Warning and content labelling will be strengthened for oral OTC drugs that contain calcium, sodium, magnesium or potassium above specific levels, as they could be harmful to patients with special sensitivities. The FDA has also proposed an extension to the sodium-labelling rules to include OTC rectal drugs containing sodium phosphates, as there may be a risk of serious electrolyte imbalances in patients with certain underlying medical conditions. The new rules came into effect on 23 April 2004, with full compliance required by 25 September 2005.

Reference:
FDA News, 25 March 2004. Available from URL: http://www.fda.gov

SHITEK TONGKAT ALI PLUS 400MG

Presence of tadalafil

Malaysia. The Drug Control Authority of Malaysia has detected the presence of tadalafil in a traditional medicine sold under the name of Shitek Tongkat Ali Plus 400mg in Malaysia. The product had a fraudulent marketing authorization number printed on its package and was manufactured by a contract manufacturer, Shitek Micro Algae Sdn Bhd. Tadalafil is a prescription drug and could pose serious health hazards if used without medical supervision. The Malaysian Drug Authority has issued a press release to advise people against using the Shitek Tongkat Ali Plus 400mg capsules. The agency has also taken action against the contract manufacturer of the product and the Pharmacy Enforcement division has conducted a nationwide surveillance to seize all batches of the product from the market.

Reference:
Communication from National Pharmaceutical Control Bureau, Ministry of Health, Malaysia, 30 April 2004.

TOLCAPONE

Marketing re-authorized, but more stringent monitoring recommended

Europe. The scientific committee of the European Medicines Evaluation Agency (EMEA) has appraised new data on the safety of tolcapone (Tasmar) and has concluded that the drug can be re-approved for marketing in Europe. Tolcapone is indicated in the treatment of Parkinson's disease. The marketing authorization for tolcapone was suspended in Europe in November 1998 following concerns about hepatotoxicity and neuroleptic malignant syndrome associated with the use of this drug. However, based on its recent safety evaluation, the committee has stated that the drug may be re-introduced into the European market under stringent monitoring for liver function effects. The committee also recommends that the drug should be contraindicated in patients with certain medical histories, including liver disease and neuroleptic malignant syndrome.

Reference:
EMEA Press Release, 23 April 2004.

TRAZODONE

Interactions with CYP3A4 inhibitors/inducers

USA. FDA and Bristol Myers Squibb have notified health-care professionals of revisions to the Clinical Pharmacology and Precautions sections of the labelling for trazodone (Desyrel) indicating the potential for interactions between trazodone and CYP3A4 inhibitors/inducers. Trazodone is indicated for the treatment of depression and appears to be metabolized by the CYP450 3A4 (CYP3A4) enzyme system (other metabolic pathways may also be involved). The metabolic clearance of trazodone could be impaired by CYP3A4 inhibitors ketoconazole, ritonavir, and indinavir, with a resultant increase in plasma trazodone level and a potential for adverse drug effects. On the other hand, CYP3A4 inducers such as

carbamazepine could enhance the metabolism of trazodone, thus reducing the plasma concentration of the drug, with a potential effect on therapeutic outcome. In one study, the short-term administration of ritonavir (200 mg twice daily, 4 doses) in 10 healthy subjects decreased the plasma clearance of a single dose of trazodone (50 mg) by 52%. Adverse effects including nausea, hypotension and syncope were observed when ritonavir and trazodone were co-administered. The co-administration of carba-mazepine (400mg/day), with trazodone, 100-300 mg daily, reduced plasma concen-trations of trazodone by 76% and 60% respectively. Careful monitoring of patients is thus necessary to see if there is a need for dose adjustment when trazodone is prescribed with any of the above drugs. The product label for trazodone has been appropriately revised to reflect the above information.

Reference:

'Dear Healthcare Professional' letter from Bristol-Myers Squibb Company, May 2004. Available from URL: http://www.fda.gov

CARVEDILOL

Reports of diarrhoea

New Zealand. The Centre for Adverse Reactions Monitoring (CARM) has received four reports of diarrhoea with carvedilol (Dilatrend), a non-cardioselective beta-blocker with alpha-blocking activity, indicated in the management of essential hypertension, angina pectoris, and as adjunctive therapy in chronic heart failure. Patients were receiving carvedilol in the dose range of 6.25 to 25mg daily. In three reports, severe diarrhoea developed within a week; and in the fourth case, the diarrhoea was moderate and began during the first month of carvedilol treatment. In all cases, symptoms improved on stopping the medicine. Diarrhoea is a recognised adverse effect of all beta-blockers. Prescribers may have to discontinue treatment with beta blockers and switch patients to alternative therapy if diarrhoea persists or gets severe. However, the drug needs to be withdrawn gradually, over two weeks, since abrupt withdrawal can precipitate rebound hyper-tension, angina or myocardial infarction, especially in individuals with ischaemic heart disease.

Reference:
Prescriber Update Review, 8 April 2004. Available from URL: http://www.medsafe.gov.nz

CYCLO-OXYGENASE-2 INHIBITORS

Reports of visual disturbances

New Zealand. The Pharmacovigilance Centre in Dunedin, New Zealand has received nine reports of visual changes associated with the use of cyclo-oxygenase-2 (COX-2) inhibitors, celecoxib (six reports) and rofecoxib (three reports). The visual disturbances included blurred vision, abnormal vision, scintillating scotomata, visual field defect and temporary blindness. In all but one report, the duration to onset from first taking the COX-2 inhibitor was within four weeks. The eyesight changes were bilateral in eight of the cases. Blurred vision, cataract, conjunctivitis, eye pain and glaucoma are listed as adverse effects in the celecoxib (Celebrex) data sheet and blurred vision in the rofecoxib (Vioxx) datasheet. In all of the eight reports patients recovered quickly on withdrawal of the COX-2 inhibitor. The visual disturbances did not recur during periods of observation of up to seven months following withdrawal. Similar events have also been reported with non-specific anti-inflammatory agents. There is evidence that the cyclo-oxygenase enzymes COX-1 and COX-2 are involved in the regulation of retinal blood flow. However, other mechanisms for the observed visual disturbances with COX-inhibitors remain to be explored. If eyesight changes occur, the anti-inflammatory medicine should be immediately withdrawn and the patient assessed for improvement of visual symptoms. Future exposure to anti-inflammatory agents should be avoided in patients with a severe eye disturbance following first exposure.

Reference:
Prescriber Update Articles, March 2004. Available from URL: http://www.medsafe.govt.nz/profs/PUarticles

FURANO-COUMARINS

Presence in a herbal preparation

UK. The Medicines and Healthcare products Regulatory Agency (MHRA) is alerting herbal interest groups to a report of a severe adverse skin reaction after a patient was prescribed an unlicensed herbal preparation containing a mixture of herbal ingredients for the treatment of eczema. The herbal preparation was prepared by the patient as a decoction in boiling water, cooled and then applied to the skin. This resulted in severe inflammation and blistering. The herbal mixture consisted of *Cnidium monnieri* fruit, *Angelica sinensis* root, *Atractylodes lancea* rhizome, *Coix lacrymajobi* seed, *Smilax glabra* tuber, *Sophora flavescens* root, *Kochia scoparia* fruit, and *Pseudolaricis kaempferi* bark. It is not possible to determine the herbal ingredient(s) responsible for the skin reaction because of the complexity of the herbal mixture. However, since the adverse reaction was similar to skin reactions with Psoralea fruit, the most likely causative ingredient is thought to be the *Cnidium monnieri* fruit. *Cnidium monnieri* fruit is reported to contain furanocoumarin derivatives, two of which, xanthotoxin and bergapten, were identified in the herbal mixture. However, it is possible that other ingredients may also have contributed to the adverse reaction. The MHRA advises caution while using any of these herbal ingredients, especially *Cnidium monnieri*, on the skin. The MHRA is in

the process of gathering more information on the extent of actual usage, nature of usage etc. before deciding on further advice and action, if any.

Reference:
Communication to Herbal Interest Groups from MHRA, 19 April 2004. Available from URL: http://www.mhra.gov.uk

LEFLUNOMIDE

Awareness and monitoring can reduce the impact of adverse effects

New Zealand. According to a recent Prescriber Update article available from Medsafe, New Zealand, serious multi-system adverse effects are possible with leflunomide, an effective disease modifying agent for rheumatoid arthritis. The adverse reactions associated with the use of this drug involve haematological, hepatic, immune, dermatological and respiratory systems. International reports include liver failure (15 cases, nine with fatal outcome), neutropenia, thrombocytopenia, thrombocytosis, severe pancytopenia, Stevens Johnson syndrome, bullous eruptions and skin necrosis, interstitial pneumonitis and pulmonary infiltration and infections due to immune response impairments including sepsis. Post-marketing experience with leflunomide estimates the frequency of severe hepatic, dermatological, respiratory, haematological and infection reactions as being very rare (less than 1 in 10 000) and for blood dyscrasias as being rare (between 1 in 1000 and 1 in 10 000). According to the article, the long half-life of leflunomide may delay resolution of some of the reactions but regular monitoring and patient education of early warning signs (e.g. easy bruising, tiredness, pallor, skin lesions, shortness of breath etc.) can reduce morbidity. To minimize the risk of serious blood and liver adverse reactions, all patients taking leflunomide should have their haematological and liver function monitored. Pre-treatment baseline values should be established for these functions first before starting therapy, every month after initiating therapy for the first six months and, every six to eight weeks thereafter. Ongoing monthly monitoring is recommended if methotrexate is used concurrently.

Reference:
Prescriber Update Articles, April 2004. Available from URL: http://www.medsafe.govt.nz/Profs/PUarticles/Arava.htm

OXANDROLONE

Warning for interaction with warfarin

USA. Savient Pharmaceuticals Inc., in consultation with US FDA has issued a letter to health professionals regarding the potential for interaction when oxandrolone, an anabolic androgenic steroid and warfarin, an anticoagulant, are prescribed together. Oxandrolone is used as adjunctive therapy to promote weight gain in patients following extensive surgery, chronic infections, etc. According to a recent clinical study, concurrent dosing of oxandrolone and warfarin might prolong the half-life of warfarin with a resultant increase in the International Normalized Ratio (INR) or Prothrombin Time (PT). When oxandrolone is prescribed to patients being treated with warfarin, doses of warfarin may need to be decreased significantly to maintain a desirable INR level and diminish the risk of potentially serious bleeding. Patients should be carefully monitored for INR or PT values and for signs and symptoms of occult bleeding.

Reference:
'Dear Healthcare Professional' letter from Savient Pharmaceuticals Inc., 20 April 2004. Available from URL: http://www.fda.gov

SHUBAO SLIMMING CAPSULES

Presence of fenfluramine and nitrosofenfluramine

UK. The Medicines and Healthcare products Regulatory Agency (MHRA) is alerting herbal interest groups and consumers about the presence of fenfluramine and nitrosofenfluramine in an unlicensed traditional Chinese medicine preparation, Shubao Slimming Capsules, supplied illegally as a slimming agent in the UK. Fenfluramine is an appetite suppressant and was banned globally in 1997 due to concerns about the drug's effect on the heart while nitrosofenfluramine is known to be toxic to the liver. Globally the illegal adulteration of slimming products with nitrosofenfluramine and fenfluramine has been associated with a large number of reports of liver toxicity. There was one report of liver failure in a patient receiving Shubao Slimming Capsules in the UK; the patient required a liver transplant. The MHRA has directed that the supply and sale of Shubao capsules

should be stopped immediately and has requested cooperation from the herbal sector in minimizing the risks to consumers posed by the illegal inclusion of fenfluramine and nitroso-fenfluramine in these capsules.

Reference:
Communication to Herbal Interest Groups from MHRA, 28 April 2004. Available from URL: http://medicines.mhra.gov.uk

STATINS

Important to measure creatine kinase levels

New Zealand. A Prescriber Update article from Medsafe, New Zealand, while referring to the risk of myopathy and rhabdomyolysis associated with the use of statins, reminds prescribers to measure creatine kinase (CK) levels in patients presenting with muscle pain or weakness. Muscle pain or weakness accompanied by a CK level more than 10 times the upper limit of normal would suggest clinical myopathy. Rhabdomyolysis, a severe form of myopathy with muscle breakdown leading to myoglobinuria, may result in renal failure and death. Monitoring helps improve outcome. CK measurements weekly and specialist advice sought if there is a moderate increase in CK levels (3-10 x upper limit of normal). Health professionals are also reminded that other concomitant medicines may increase risk of myopathy, particularly if they can cause myopathy on their own (e.g. fibrates). Such a potentiation of risk could also occur when the concomitant drugs are potent inhibitors of the CYP 3A4 enzyme system (e.g. erythromycin, itraconazole, amiodarone, verapamil) because several statins such as simvastatin and atorvastatin are CYP 3A4 substrates. To minimize the risk of interaction, lower starting doses of simvastatin and atorvastatin should be used in patients already being treated with fibrates, cyclosporine, amiodarone, verapamil and other potent CYP 3A4 inhibitors; if a patient is already on statins, the dose of statins should be reduced before starting concomitant therapy with other interacting drugs.

Reference:
Prescriber Update Articles, May 2004. Available from URL: http://www.medsafe.govt.nz/profs/PUarticles/Statinmyop.htm

TEGASEROD

Warning about

- serious consequences of diarrhoea, including hypo-volemia, hypotension, and syncope have been reported in clinical studies and during marketed use of tegaserod (Zelnorm);
- rare cases of ischaemic colitis and other forms of intestinal ischaemia have been reported in patients receiving tegaserod during marketed use of the drug;
- tegaserod should be discontinued immediately in patients who develop hypotension or syncope, and in patients who develop symptoms of ischaemic colitis such as rectal bleeding, bloody diarrhoea or new or worsening abdominal pain;
- patients should be advised to stop taking tegaserod in case of above symptoms and should seek medical advice if they experience new or worsening abdominal pain, with or without rectal bleeding and/or blood in the stool.

References:
1. *'Dear Healthcare Professional' letter from Novartis Pharmaceuticals Corporation, 26 April 2004. Available from URL: http://www.fda.gov/medwatch*
2. *'Dear Healthcare Professional' letter from Novartis*