WHO PHARMACEUTICALS NEWSLETTER

World Health Organization

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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The WHO Pharmaceuticals Newsletter provides you with the latest information on the safety of medicines and legal actions taken by regulatory authorities across the world. It also provides signals from the Uppsala Monitoring Centre's SIGNAL document.

In addition to the usual features, this issue includes the summary of discussions from the eleventh meeting of the WHO Advisory Committee on Safety of Medicinal Products (ACSoMP).

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Bupropion

Serious cardiovascular adverse events

Australia. The Therapeutic Goods Administration (TGA) informs that the Product Information for bupropion is being updated to provide further information about the risk of serious cardiovascular adverse events.

Bupropion is a selective inhibitor of the neuronal reuptake of catecholamines, noradrenaline and dopamine. It is registered for use in Australia as a short-term adjunctive therapy, used in conjunction with counselling and abstinence, for nicotine dependence to assist in smoking cessation.

The Product Information (PI) for bupropion had previously contained information regarding hypertension. However, the TGA has identified postmarket spontaneous reports of more serious cardiovascular events, including myocardial infarction. To address this, the TGA is working closely with the manufacturer to update and strengthen the precautions for serious cardiovascular adverse events in the PI.

The updated information will advise that there have been reports of patients receiving bupropion (alone and in combination with nicotine replacement therapy) experiencing severe hypertension requiring acute treatment, in patients both with and without pre-existing hypertension.

The updated information will also advise that there is limited clinical experience establishing the safety of bupropion in patients with a recent history of myocardial infarction or unstable heart disease. Therefore, health professionals should exercise care if using bupropion in such patients.

It is recommended that blood pressure be monitored while the patient is taking bupropion, especially in patients with pre-existing hypertension, and consideration be given to discontinuing treatment if a clinically significant increase is observed.

A higher rate of hypertension has been observed when treatment with bupropion is combined with use of nicotine transdermal system products (patches).

If bupropion is used in combination with nicotine patches, caution must be exercised and weekly monitoring of blood pressure is recommended.

Reference: *Medicine Safety Update. October* 2014. (*www.tga.gov.au*)

Diclofenac

Arteriothrombotic events

Australia. The TGA informs that the Product Information documents for prescription-only diclofenac have been updated to provide further information about the increased risk of arteriothrombotic events.

Diclofenac is a non-steroidal anti-inflammatory drug (NSAID). Prescription-only products are available in oral and rectal forms.

Information regarding arteriothrombotic events was previously included in the precaution and adverse reaction sections of the Product Information (PI). However, the updated PI includes details from meta-analyses of individual participant data from randomised trials by the Coxib and traditional NSAID Trialists' Collaboration that estimated, in comparison with placebo, use of diclofenac caused about three additional major vascular events per 1000 patients per year. This information was derived from trials involving long-term (more than 28 days) treatment with high-dose diclofenac (150 mg/day).

To minimise risks, the lowest effective daily dose should be used for the shortest duration necessary to control symptoms.

Patients with cardiovascular disease or other risk factors may be at greater risk. The TGA is undertaking a review of all NSAIDs with regards to their association with cardiovascular risk.

Reference: *Medicine Safety Update. August* 2014. (*www.tga.gov.au)*

Risk of Major Heart and Stroke Related Adverse Events

Canada. Health Canada has reviewed the safety of diclofenac and has found that diclofenac is associated with an increased risk of heart and stroke related adverse events that is comparable to COX-2 inhibitors, and that this risk should be considered when prescribing or taking diclofenac.

Health Canada informs that the overall benefits of diclofenac continue to outweigh the risks, when used as recommended.

However, in order to further reduce the risks associated with diclofenac, additional information is being added to the prescribing information for diclofenac-containing products, which includes:

- Specifying that diclofenac at a higher dose (150 mg per day) is associated with an increased risk of heart and stroke related adverse events that is comparable to COX-2 inhibitors.
- Reducing the maximum daily dose for diclofenac from 150 mg to 100 mg for all indications, excluding VOLTAREN RAPIDE which allows for a 200 mg dose only

on the first day of treatment for dysmenorrhea.

- Recommending that for patients with a high risk of developing heart and stroke related adverse events, other treatment options that do not include NSAIDs, particularly COX-2 inhibitors and diclofenac, should be considered first.

Reference: *Health Canada, Important Safety Information. 06 October 2014. (www.canada.gc.ca)*

Methylphenidate

Priapism

Australia. The TGA warns that in very rare cases, treatment with methylphenidate may potentially lead to prolonged and sometimes painful erections (priapism).

Methylphenidate is a central nervous system stimulant and is indicated for the treatment of attention deficit hyperactivity disorder (ADHD). A US Food and Drug Administration review of methylphenidate products resulted in priapism being added as a class warning to the drug's labelling. Subsequent investigation by the TGA found that, while there had been no reports of this adverse event in Australia, the risk of untreated priapism was potentially serious.

A precaution for priapism has recently been added to the Australian Product Information (PI) for methylphenidate. While this risk applies to all use in males, the greatest concern is regarding pre-pubertal boys, who might not recognise the problem or may be too embarrassed to seek help if it occurs. Health professionals should consider educating parents and caregivers of pre-pubertal boys being treated with methylphenidate about this issue, while reassuring them that it is very rare.

Priapism can develop some time after drug initiation, often subsequent to an increase in dose, and has also been observed during a period of methylphenidate withdrawal.

Health professionals who are considering switching patients to another drug due to this issue are advised that atomoxetine, which is also used to treat ADHD, has been associated with priapism. The PI for atomoxetine lists painful or prolonged erection and male genital pain as potential, but very rare, adverse events.

Reference: *Medicine Safety Update. October* 2014. (*www.tga.gov.au*)

Omalizumab

Slightly elevated risk of cardiovascular and cerebrovascular serious adverse events

USA. The US Food and Drug Administration (FDA) suggests a slightly increased risk of problems involving the heart and blood vessels supplying the brain among patients being treated with the asthma drug omalizumab than in those who were not treated with the drug following a review of safety studies. As a result, FDA has added information about these potential risks to the drug label.

Omalizumab is an injectable medicine for patients 12 years of age and older with moderate to severe persistent allergic asthma whose asthma symptoms are not controlled by asthma medicines called inhaled corticosteroids.

The review found no difference in the rates of cancer between those patients being treated with and those who were not being treated with omalizumab. However, due to limitations in the 5-year study, FDA cannot rule out a potential risk of cancer with omalizumab, so this information was added to the Warnings and Precautions section of the drug label.

Reference: *FDA Safety Communications, US FDA, 26 September 2014. (www.fda.gov)*

Topiramate

Visual field defects

New Zealand. The New Zealand Medicines and Medical Devices Safety Authority (MEDSAFE) has informed that there has been reports of Visual field defects in patients receiving topiramate.

Topiramate is an anticonvulsant (antiepilepsy) drug. The drug had previously been used off-label for weightloss. In clinical trials, most of the side events were reversible after topiramate discontinuation in patients receiving topiramate independent of elevated intraocular pressure.

Visual Field Defects are a recognised adverse reaction for topiramate as described in the Adverse Effects section of the data sheet. Based on cumulative data from a recent review of post-marketing safety databases, and clinical trials, this additional safety Information has now been added in the Warning and Precautions section of the data sheet to increase awareness of this serious risk.

Reference: *Safety Information, MEDSAFE, 05 August 2014. (www.medsafe.govt.nz/)*

Valproate

Fetal exposure and cognitive impairment

Australia. The TGA has reviewed updated information regarding the association between use of valproate during pregnancy and cognitive impairment in children.

Valproate is an anticonvulsant that is indicated for the treatment of primary generalised epilepsy and partial epilepsy. It is also indicated for the treatment of mania, where other therapy has proven inadequate or is inappropriate.

Earlier studies examined the effect of fetal exposure to valproate on cognitive outcomes in children and these risks are reflected in the Australian Product Information (PI).

In 2013, the Neurodevelopmental Effects of Antiepileptic Drugs (NEAD) study published its final analysis, which found that fetal valproate exposure had dose-dependent associations with reduced cognitive abilities across a range of domains at six years of age.

Meanwhile, another study found a link between use of valproate during pregnancy and autism spectrum disorders and childhood autism in the offspring, even after adjusting for maternal epilepsy.

The Product Information for valproate contains a warning about autism spectrum disorders and information about fetal exposure and the risk of developmental delay in the Use in Pregnancy section. However, the TGA's review of the updated information in the NEAD study has concluded that the information about cognitive impairment should be updated to show that cognitive deficits have been observed at six years of age.

The sponsor has agreed to update the PI and intends to also incorporate any recommendations that may result from an ongoing review being conducted in the European Union.

Reference: *Medicine Safety Update. October* 2014. (*www.tga.gov.au)*

Azathioprine

Serious Brain Infection (Progressive Multifocal Leukoencephalopathy)

Canada. Health Canada has warned that there is evidence that suggests a link between azathioprine and Progressive Multifocal Leukoencephalopathy (PML), a rare and serious brain infection.

Azathioprine is an immunosuppressive drug used in organ transplantation and autoimmune diseases. It is used alone or in combination with other immunosuppressive therapy to prevent rejection following organ transplantation, and to treat an array of autoimmune diseases. It is also an important therapy and steroid-sparing agent for inflammatory bowel disease (such as Crohn's disease and ulcerative colitis) and for multiple sclerosis.

A safety review was conducted to evaluate the available information regarding the potential risk of developing PML with azathioprine.

This review was conducted because several cases of PML had been reported worldwide in patients who had received azathioprine.

It is difficult to determine to what extent azathioprine contributes to PML. However, health-care professionals and patients should be aware of the possibility for PML to develop with azathioprine.

Health Canada is working with manufacturers to update the product information for Azathioprine.

Reference: *Health Canada, Important Safety Information. September 30 2014. (www.canada.gc.ca)*

Bo Ying Compound ®

Risk of lead poisoning

USA. The US FDA warns parents and caregivers not to use "Bo Ying compound" manufactured by Eu Yan Sang (Hong Kong) Ltd. due to the potential lead poisoning risk associated with the product.

FDA learned of this risk from the New York City Department of Health & Mental Hygiene after the product was tested and found to contain high levels of lead. FDA has received one adverse event report of lead poisoning in an 18-month-old child who was given this product.

The powdered product is marketed in retail outlets and online for use in infants and children for treatment of a variety of conditions including influenza, fever, sneezing, and nasal discharge. The product is labeled in Chinese and English.

Exposure to lead can cause serious damage to the central nervous system, the kidneys, and the immune system. In children, chronic exposure to lead, even at low levels, is associated with impaired cognitive function, including reduced IQ, behavioral difficulties, and other problems.

Reference: *FDA Safety Communications, US FDA, 26 September 2014 (www.fda.gov).*

Bromocriptine

Restricted use in preventing or stopping lactation

Europe. The European Medicines Agency (EMA's) Coordination Group for Mutual Recognition and Decentralised Procedures – Human (CMDh) has endorsed by majority recommendations on the use of oral bromocriptine containing medicines to prevent or suppress breast milk production (lactation) after childbirth.

A review of oral bromocriptine was initiated at the request of France in 2013 of rare but potentially serious or fatal side effects, particularly cardiovascular side effects (such as heart attack and stroke), neurological side effects such as seizures (fits) and psychiatric side effects (such as hallucinations and manic episodes). The review was first conducted by the Pharmacovigilance Risk Assessment Committee (PRAC).

Since lactation is a natural process that eventually stops if the infant is not breastfed, and other means of management are available, the French medicines agency (ANSM) asked the EMA to review the medicines and see if the benefits of such use still outweighed the risks.

The PRAC recommendations were sent to the CMDh, which adopted a final position.

The PRAC's recommendations are based on a review of the available evidence of safety and efficacy of oral bromocriptine for prevention and suppression of lactation.

The CMDh agreed that the medicines should only be used for this purpose (in strengths up to 2.5 mg) when there are compelling medical reasons for stopping lactation, such as the need to avoid further distress after loss of the baby during or just after childbirth, or in mothers with HIV infection, who should not breastfeed.

Bromocriptine should not be used routinely for preventing or stopping milk production, and must not be used in women at increased risk of serious side effects, including women with various disorders that increase blood pressure or

who have or have had heart disease or severe psychiatric disorders. Blood pressure should be monitored so that early signs of an increase can be detected and treatment stopped immediately.

As the CMDh position on bromocriptine was adopted by majority vote, it will now be sent to the European Commission, which will take an EU-wide legally binding decision.

***Reference**: Press Release, EMA, 21 August 2014 (www.ema.europa.eu)*

Denosumab

Updated recommendations on minimising the risk of osteonecrosis of the jaw and hypocalcaemia

UK. The Medicines and Health-care products Regulatory Agency (MHRA) has warned that denosumab is associated with a risk of osteonecrosis of the jaw (ONJ) and with a risk of hypocalcaemia. The risk of hypocalcaemia increases with the degree of renal impairment when using denosumab 120mg for cancer or denosumab 60mg for osteoporosis.

Denosumab 120mg solution for injection is given once every 4 weeks to prevent skeletal related events (pathological fracture, radiation to bone, spinal cord compression, or

To minimize the risk of ONJ and hypocalcaemia, MHRA recommends that calcium levels are to be closely monitored in patients receiving this drug.

Good oral hygiene, routine dental check-ups, and immediate report of any oral symptoms such as dental mobility, pain, or swelling to a doctor and dentist should be made.

***Reference:** Drug Safety Update. September 2014. (www.mhra.gov.uk)*

Ferumoxytol

Risk of serious hypersensitivity reactions

UK. The MHRA has declared that ferumoxytol is now contraindicated in patients with any known history of drug allergy, including hypersensitivity to other parenteral iron products.

This warning came as a result of re-evaluation of the benefits and risks of ferumoxytol. The evaluation focused on the cumulative reports of serious hypersensitivity reactions including life-threatening and fatal anaphylactic reactions to the drug.

Many of the patients who had a life-threatening or fatal anaphylactic reaction also had

hypersensitivity is increased in patients with immune or inflammatory conditions (e.g. systemic lupus erythematosus, rheumatoid arthritis) and in patients with a history of severe asthma, eczema, or other atopic allergy. In these patients, ferumoxytol should only be used if the benefits are clearly judged to outweigh the risks.

Ferumoxytol should only be administered as an intravenous infusion, in 50 to 250 ml of sterile 0.9% sodium chloride or sterile 5% glucose, and over a minimum period of 15 minutes.

Careful monitoring of patients for signs and symptoms of hypersensitivity reactions, including monitoring of blood pressure and pulse, during and for at least 30 minutes after the infusion is important.

***Reference:** Drug Safety Update. September 2014. (www.mhra.gov.uk)*

Measles, Mumps, Rubella, Varicella (MMRV) vaccine

Reminder of associated fever and febrile convulsion

Australia. The TGA has reminded health professionals that to minimise the risk of fever and febrile convulsion, MMRV vaccine should not be administered as the first dose