WHO PHARMACEUTICALS NEWSLETTER

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

The aim of the Newsletter is to disseminate information on the safety and efficacy of pharmaceutical products, based on communications received from our network of "drug information officers" and other sources such as specialized bulletins and journals, as well as partners in WHO. The information is produced in the form of résumés in English, full texts of which may be obtained on request from:

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No. 2, 2014

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.

Printed by the WHO Document Production Services, Geneva, Switzerland

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Regulatory Matters

Safety of medicines

Signal

Aliskiren, angiotensin-converting enzyme inhibitors or angiotensin receptor blockers

New warnings regarding blood pressure drugs

Canada. Health Canada informed health-care professionals and patients of the risks associated with combining more than one of the following blood pressure medicines: aliskiren (renin inhibitor), angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs). Recent studies demonstrated that any combination of aliskiren, ACEIs or ARBs increases the risks of hypotension, hyperkalemia and kidney problems.

Furthermore, aliskiren should not be taken in combination with ACEIs or with ARBs in patients with diabetes or kidney disease due to the additional risks of stroke and syncope in these patients. The product labels have been updated to better reflect the new recommendations regarding the safe use of these medicines.

(See WHO Pharmaceuticals Newsletter No.3, 2012 for new warning and contraindication in the US, No.1, 2012 for contra-indication in patients with diabetes taking an ACE inhibitor or an ARB in Canada and No.2, 2012 in Europe).

Reference:
Advisories, Warnings and Recalls, Health Canada, 4 February 2014 (*www.hc-sc.gc.ca*).

Azathioprine and mercaptopurine

Association with Hepatosplenic T-Cell Lymphoma

Canada. Triton Pharma Inc. and Teva Canada Ltd., in consultation with Health Canada, informed the association between the use of purine antagonists azathioprine (Imuran®) or mercaptopurine (Purinethol®) and the development of hepatosplenic T-cell lymphoma (HSTCL), a rare, aggressive and often fatal cancer, mostly in patients where it is used for inflammatory bowel disease (IBD). Azathioprine is a drug used to treat adult rheumatoid arthritis and help prevent kidney transplant rejection. Mercaptopurine is a drug approved to treat leukemias. Azathioprine or mercaptopurine monotherapies are not authorized by Health Canada for the treatment of IBD.

Azathioprine and mercaptopurine labels were updated for HSTCL and physicians should discuss the currently available information regarding risks and benefits of these treatments with their patients.

Reference:
Advisories, Warnings and Recalls, Health Canada, 27 March 2014 (*www.hc-sc.gc.ca*).

Cetuximab

Importance of establishing wild type *RAS* (*KRAS* and *NRAS*) status before treatment of metastatic colorectal cancer

UK. The Medicines and Healthcare products Regulatory Agency (MHRA) announced that, in the treatment of metastatic colorectal cancer, inferior overall survival, progression-free survival, and objective response rates have been shown in people with *RAS* mutations (at exons 2, 3, and 4 of *KRAS* and *NRAS*) who received cetuximab (Erbitux®) in combination with FOLFOX4 (oxaliplatin-containing) chemotherapy versus FOLFOX4 alone. Cetuximab is now indicated for the treatment of people with epidermal growth factor receptor (EGFR)-expressing, *RAS* wild-type metastatic colorectal cancer in combination with irinotecan or oxaliplatin based chemotherapy or as a single agent. Evidence of wild type RAS status at these exons is required before initiating treatment with cetuximab alone or in combination with chemotherapy in metastatic colorectal cancer. Cetuximab combined with oxaliplatin-containing chemotherapy is now contraindicated in people with metastatic colorectal cancer who have mutant RAS at these exons or unknown RAS status. Cetuximab (Erbitux®) is a treatment for people with metastatic colorectal cancer.

It is also advised that *RAS* mutation status should be determined by an experienced laboratory using a validated test method. Prescribing information for cetuximab in the treatment of people with squamous-cell carcinoma of the head and neck is not changed by the new information from this analysis.

Reference:
Drug Safety Update, February 2014, Volume 7, issue 7, A1 MHRA, (*www.mhra.gov.uk*).

Combined hormonal contraceptives

Review confirms risk of venous thromboembolism is small

UK. The MHRA announced that a review of the latest evidence on the risk of thromboembolism in association with combined hormonal contraceptives (CHCs) concluded that:

- the risk of blood clots with all low-dose CHCs is small
- there is good evidence that the risk of venous thromboembolism (VTE) may vary between products, depending on the progestogen
- CHCs that contain levonorgestrel, norethisterone, or norgestimate have the lowest risk of VTE
- the benefits of any CHC far outweigh the risk of serious side effects
- prescribers and women should be aware of the major risk factors for thromboembolism, and of the key signs and symptoms

Health-care professionals are advised to consider such factors and remain vigilant for signs & symptoms.

Health-care professionals are also advised to remind women to read the Patient Information Leaflet that accompanies each pack of CHCs, to read the information provided in user card and information sheet and to mention that they are using a CHC if asked whether they are taking any medicines.

Reference:
Drug Safety Update, February 2014, Volume 7, issue 7, A2 MHRA, (*www.mhra.gov.uk*).

Diacerein-containing medicines

Recommendations to restrict the use of diacerein-containing medicines

Europe. The Co-ordination Group for Mutual Recognition and Decentralised Procedures – Human (CMDh) endorsed recommendations to restrict the use of diacerein-containing medicines in order to manage the risks of severe diarrhoea and effects on the liver. Due to the risks associated with severe diarrhoea, diacerein is no longer recommended in patients aged 65 years and above. It is also advised that patients start treatment on half the normal dose (i.e. 50 mg daily instead of 100 mg) and should stop taking diacerein if diarrhoea occurs.

In addition, diacerein-containing medicines must not be used in any patient with liver disease or a history of liver disease, and doctors should be monitoring their patients for early signs of liver problems. Doctors should also note that, based on available data, the use of diacerein is to be limited to treating symptoms of osteoarthritis affecting the hip or knee. Treatment should only be started by doctors experienced in treating osteoarthritis.

These recommendations are based on the review of the benefits and risks of diacerein conducted by the EMA's Pharmacovigilance and Risk Assessment Committee (PRAC) and follow concerns raised by the French medicines agency (ANSM) about diacerein's gastro-intestinal and liver effects.

Diacerein is a slow-acting medicine of the class 'anthraquinones' used to treat joint diseases such as osteoarthritis.

Reference:
Press release, EMA, 21 March 2013 (*www.ema.europa.eu*).

Doripenem

Risk when used to treat pneumonia on ventilated patients

USA. The U.S. Food and Drug Administration (FDA) concluded that doripenem (Doribax®), an antibacterial drug used to treat patients who develop pneumonia while on ventilators, carries an increased risk of death and lower clinical cure rates compared to use of imipenem and cilastatin for injection (Primaxin®). Doripenem is not approved to treat any type of pneumonia.

Health-care professionals should consider whether the benefits of doripenem treatment are likely to exceed its potential risks in patients who develop pneumonia while on ventilators. Doripenem is still considered safe and effective for its FDA-approved indications - treatment of adults with complicated intra-abdominal infections and complicated urinary tract infections, including kidney infections (pyelonephritis).

(See WHO Pharmaceuticals Newsletters No. 2, 2012 for higher mortality rate and a lower clinical cure rate observed during a comparative clinical trial in Canada)

References:
FDA Drug Safety Communication, US FDA 5 March 2014 (*www.fda.gov*).

Lithium

Risk of hypercalcemia and hyperparathyroidism

Canada. Health Canada informed health-care professionals that it has reviewed the available evidence and scientific

literature, and determined that lithium therapy can cause hypercalcemia which may or may not be accompanied with hyperparathyroidism. The benefits of this drug in the treatment of bipolar disorder continue to outweigh the known risks of this drug.

Lithium is used in the treatment of manic episodes of manic-depressive illness. It is used to treat acute manic episodes, and as a long-term therapy to reduce their frequency and severity.

Health Canada recommends health-care professionals to consider calcium blood levels before starting a patient on lithium treatment, again six months after initiation of the drug, and on an annual basis after that, in long-term treatment. It is also recommended to consider measuring parathormone blood level to identify or rule out hyperparathyroidism if necessary.

Reference:
Advisories, Warnings and Recalls, Health Canada, 5 February 2014 (*www.hc-sc.gc.ca*).

Methysergide-containing medicines

New recommendations follow concerns over association with fibrosis

Europe. The EMA recommended restricting the use of methysergide due to concerns that it could cause fibrosis, a condition in which fibrous tissue accumulates in the body's organs potentially damaging them. Methysergide medicines are now only to be used for preventing severe intractable migraines and cluster headaches when standard medicines have failed.

In addition, treatment should only be started and supervised by a specialist doctor with experience in treating migraine and cluster headaches. Patients should also be screened for fibrosis at the start of treatment and should have additional screenings every 6 months. Treatment must be discontinued if symptoms of fibrosis occur.

The Agency's Committee for Medicinal Products for Human Use (CHMP), which conducted the review, noted that these recommendations were necessary due to the reports of fibrosis seen with methysergide and other medicines of the same class (ergot derivatives). The symptoms of fibrosis often take some time to appear and without screening, the diagnosis may come too late to prevent severe (and potentially life-threatening) damage to organs .

The Committee noted that there is some evidence of a clinically relevant effect of methysergide when used for prevention in patients who regularly get migraines and cluster headaches and for whom treatment options are limited. Methysergide has also been used for treating diarrhoea caused by carcinoid disease. However, there were no data to support this use and methysergide should therefore no longer be used in carcinoid disease.

Methysergide is a medicine that belongs to the class 'ergot alkaloids' that has been used in the EU for preventing migraines (with or without aura) and other types of throbbing headaches.
Reference:
Press release, EMA, 21 February 2013 (*www.ema.europa.eu*).

Orlistat

Interaction with antiretroviral HIV medicines

UK. The MHRA announced that orlistat may theoretically reduce the absorption of antiretroviral HIV medicines. This may be due to retention of lipophilic medicines in the gastrointestinal tract or reduced gastrointestinal tract transit time. This interaction could negatively affect the efficacy of antiretroviral HIV medications. Reports have been received of suspected interactions between orlistat and efavirenz, and between orlistat and lopinavir. However, the theoretical interaction mechanism described above could also apply to other antiretroviral medicines.

Health-care professionals are advised to initiate orlistat treatment only after careful consideration of the possible impact on efficacy of antiretroviral HIV medicines. Pharmacists should advise people who take antiretroviral HIV medicines to consult their doctor before taking non-prescription 60 mg orlistat

Orlistat is a potent, specific, and long-acting inhibitor of gastrointestinal lipases which decreases the amount of fat absorbed from the diet. Orlistat is indicated for weight loss in combination with a low-calorie, low-fat diet. It is available as 120 mg capsules under the brand name Xenical® and as 60 mg capsules under the brand name Alli™. Xenical is only available with a prescription, whereas Alli™ is available without a prescription under the supervision of a pharmacist.

Reference:
Drug Safety Update, March 2014, Volume 7, issue 8, A1 MHRA, (*www.mhra.gov.uk*).

Quetiapine

Risk of QT prolongation

Australia. The Therapeutic Goods Administration (TGA) advised health-care professionals that the Product Information (PI) for quetiapine (Seroquel® and generics) was updated to include additional information regarding risks of QT prolongation. Quetiapine is an atypical antipsychotic drug indicated for the treatment of schizophrenia and bipolar disorder.

The PI for quetiapine products now advises, particularly in elderly patients, to avoid concomitant treatment with antipsychotics and other drugs that are known to prolong the QT interval. These include:

- Class IA antiarrhythmics (such as disopyramide)
- Class III antiarrhythmics (such as amiodarone and sotalol)
- antipsychotics (such as ziprasidone, chlorpromazine and haloperidol)
- antibiotics (such as erythromycin)
- others (such as citalopram, pentamidine and methadone).

The updated information also advises that quetiapine should be avoided in circumstances that may increase the risk of torsades de pointes and/or sudden death, including a history of cardiac arrhythmias, hypokalaemia or hypomagnesaemia, and congenital prolongation of the QT interval.

Additionally, the PI has also been updated to include further information about the risk of venous thromboembolism (VTE), akathisia, neutropenia.

Health-care professionals are encouraged to review the latest PI for quetiapine and particularly the updated information regarding QT prolongation, VTE, akathisia and neutropenia in the precautions section.

Reference:
Medicines Safety Update Vol 5, No. 1, February 2014. (www.tga.gov.au).

Strontium ranelate

Remain available but with further restrictions

Europe. The EMA concluded its review of strontium ranelate (Protelos® and Osseor®) and recommended further restricting the use of the medicine to patients who cannot be treated with other medicines approved for osteoporosis. In addition these patients should continue to be evaluated regularly by their doctor and treatment should be stopped if patients develop heart or circulatory problems, such as uncontrolled high blood pressure or angina. As recommended in a previous review, patients who have a history of certain heart or circulatory problems, such as stroke and heart attack, must not use the medicine.

These final recommendations from the Agency's Committee for Medicinal Products for Human Use (CHMP) come after initial advice from the Pharmacovigilance Risk Assessment Committee (PRAC) to suspend the medicine due to its cardiovascular risk.

The CHMP noted that study data showed a beneficial effect in preventing fractures, including in patients at high risk of fracture. In addition, available data do not show evidence of an increased cardiovascular risk with strontium ranelate in patients who did not have a history of heart or circulatory problems. The CHMP considered that the cardiovascular risk in patients taking strontium ranelate can be managed by restricting its use to patients with no history of heart and circulatory problems and limiting its use to those who cannot take other medicines approved for the treatment of osteoporosis. In addition, patients treated with strontium ranelate should be screened and monitored regularly, every 6 to 12 months.

Additional risk minimisation measures include providing educational material to prescribers to ensure that only the appropriate patients are treated with the medicine. Importantly, the company is required to conduct further research to demonstrate the effectiveness of the new measures.

Strontium ranelate is authorised in the EU to treat severe osteoporosis in women who have been through menopause and who are at high risk of fracture to reduce the risk of fractures' of the spine and the hip. It is also used to treat severe osteoporosis in men who are at high risk of fracture.

Reference:
Press release, EMA, 21 February 2013 (*www.ema.europa.eu*).

Saxagliptin

Review heart failure risk

USA. The US FDA requested clinical trial data from the manufacturer of saxagliptin (Onglyza® and Kombiglyze™ XR) to investigate a possible association between use of the type 2 diabetes drug and heart failure. The US FDA's request resulted from a study published in the New England Journal of Medicine (NEJM), which reported an increased rate of hospitalization for heart failure, when the heart does not pump blood well enough, with use of saxagliptin compared to an inactive treatment. The study did not find increased rates of death or other major cardiovascular risks, including heart attack or stroke, in patients who received saxagliptin. The manufacturer is expected to submit the trial data to FDA by early March 2014, after which FDA will conduct a thorough analysis and report findings publicly.

At this time, the US FDA considered information from the NEJM study to be preliminary. Analysis of the saxagliptin clinical trial data is part of a broader evaluation of all type 2 diabetes drug therapies and cardiovascular risk.

Saxagliptin is used along with diet and exercise to lower blood sugar in adults with type

St John's wort and hormonal contraceptives, including implants

Reduced contraceptive effect

UK. The Medicines and Healthcare products Regulatory Agency (MHRA) announced that St John's wort interacts with hormonal contraceptives. This interaction reduces the effectiveness of these contraceptives and increases the risk of unplanned pregnancy. This applies to all hormonal contraceptives except intrauterine devices, for which there are currently no data

St John's wort (*Hypericum perforatum* L.) is a herbal medicine traditionally used to relieve slightly low mood and mild anxiety.

The MHRA received two Yellow Card reports in the last quarter of 2013 of suspected interactions in women with implanted contraceptives containing etonogestrel (Nexplanon® and Implanon®). These women started taking St John's wort and then had unplanned pregnancies.

There are warnings about these interactions and their consequences in the product information provided with all contraceptives and the authorised St John's wort products. Some unlicensed contraceptives except intrauterine devices, for which there are currently no data. It is also advised to encourage women to read the Patient Information Leaflet that comes with their hormonal contraceptive.

Reference:
Drug Safety Update, March 2014, Volume 7, issue 8, A2 MHRA, (www.mhra.gov.uk).

Testosterone Products

Investigating risk of cardiovascular events

USA. The US FDA is investigating the risk of stroke, heart attack, and death in men taking FDA-approved testosterone products. The US FDA is monitoring this risk and decided to reassess this safety issue based on the recent publication of two separate studies that each suggested an increased risk of cardiovascular events among groups of men prescribed testosterone therapy. The US FDA provided this alert while it continues to evaluate the information from these studies and other available data. The US FDA will communicate final conclusions and recommendations when the evaluation is complete.

Testosterone is a hormone essential to the development of male growth and masculine characteristics. Testosterone products are FDA-approved