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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This Newsletter is also available on our Internet website:
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No. 6, 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 based on information derived from Individual Case Safety Reports (ICSRs) available in the WHO Global ICSR database, VigiBase®.

The current issue also includes the recommendations from the 16th International Conference of Drug Regulatory Authorities (ICDRA) held in Brazil, 26 – 29 August 2014.

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Agomelatine

Risk of liver toxicity

Europe. The European Medicines Agency (EMA) recommended that further measures for agomelatine (Valdoxan® and Thymanax®) should be put in place to minimise the risk of liver toxicity. Agomelatine is used to treat major depression in adults.

A patient booklet will be distributed to all patients taking agomelatine so that they are aware of the risk to the liver and the signs of liver problems to look out for. This booklet also includes information on the importance of monitoring liver function.

Warnings in the product information will also be strengthened to emphasise that liver function tests should be performed in patients both before starting the medicine and regularly during treatment.

Health-care professionals should follow these recommendations:

- Baseline liver function tests should be performed in every patient and treatment should not be started in patients with transaminases exceeding 3 times the upper limit of normal.
- Liver function must be monitored regularly during treatment, at 3, 6, 12 and 24 weeks and regularly thereafter when clinically indicated.
- Treatment must be discontinued immediately if the increase in serum transaminases exceeds 3 times the upper limit of normal, or if patients present with symptoms or signs of potential liver injury.
- Patients should be informed of the symptoms of potential liver injury and the importance of liver function monitoring, and should be advised to stop taking agomelatine immediately and to seek urgent medical advice if these symptoms appear.

Reference:
Press release, EMA, 26 September 2014 (*www.ema.europa.eu*)

Azithromycin

Drug Reaction/Rash with Eosinophilia and Systemic Symptoms (DRESS)

Canada. Health Canada published that a safety review was initiated to evaluate the possible link between a medical condition called DRESS which stands for Drug Reaction/Rash with Eosinophilia and Systemic Symptoms, and the antibiotic azithromycin (Zithromax®, Zmax® and its generics). This review was prompted from an adverse reaction report submitted to Health Canada.

Azithromycin belongs to a group of antibiotics called macrolides and is available as an oral liquid, a tablet and an injectable product.

DRESS describes a group of rare but serious and potentially life-threatening adverse reactions to medications. These reactions usually occur two weeks to two months after starting a medication. Patients may experience symptoms such as a fever, a severe skin rash with swollen face or peeling of the skin over large areas of the body. Abnormal changes in blood cells or organ function such as the liver and kidney may also occur. The reasons why DRESS can occur with some medications are unknown.

The current available evidence suggests the possibility that DRESS may occur with azithromycin use. Furthermore, DRESS is a known risk for a similar antibiotic, clarithromycin. Other serious, rare, allergic skin reactions such as Toxic Epidermal Necrolysis (TEN) and Stevens-Johnson Syndrome (SJS) are described in the prescribing information for azithromycin. Common features between all three conditions may make it more difficult for early diagnosis.

The prescribing information for azithromycin has been updated to include the possible risk of DRESS.

It is important for health-care professionals and patients to be aware of the possibility of these rare serious reactions, and for steps to be taken for early detection of DRESS due to the fact that the treatment of TEN and SJS is different from DRESS.

Reference:
Advisories, Warnings and Recalls, Health Canada, 21 October 2014 (*www.hc-sc.gc.ca*)

Basiliximab

Indicated for renal transplantation only

UK. The Medicines and Healthcare Products Regulatory Agency (MHRA) informed that basiliximab (Simulect®) is indicated for preventing acute organ rejection only for allogeneic renal transplantation in patients receiving organ transplantation for the first time.

A European regulatory review investigated the safety and efficacy of basiliximab for off-label use in heart transplantation. This review was triggered by three unexplained deaths in Sweden in patients who received basiliximab for heart transplantation. All three patients had signs and

symptoms of thromboembolic events and potential cardiac disorders.

The review found no adequately powered randomised studies of basiliximab in heart transplantation. The clinical trials that have been done in heart transplantation did not prove basiliximab to be effective. Furthermore, serious cardiac side effects such as cardiac arrest, atrial flutter, and palpitations were observed more frequently with basiliximab than with other induction agents. Therefore a new warning has been included in the basiliximab product information regarding the lack of proven safety and efficacy in heart transplantation.

Reference:
Drug Safety Update, October 2014, Volume 8, issue 3, S1 MHRA, (*www.mhra.gov.uk*)

Clopidogrel

Association of with acquired haemophilia

Egypt. Egyptian Pharmaceutical Vigilance Center (EPVC) has warned about the association of clopidogrel with acquired haemophilia.

Clopidogrel is an oral, thienopyridine class antiplatelet agent; it is indicated for the prevention of atherothrombotic events in myocardial infarction, ischaemic stroke, established peripheral arterial disease, acute coronary syndrome including non-ST segment elevation myocardial infarction and unstable angina, and ST segment elevation acute myocardial infarction with aspirin in medically treated patients eligible for thrombolytic therapy. Clopidogrel is also indicated in combination with aspirin for the prevention of atherothrombic and thromboembolic events in atrial fibrillation in patients unsuitable for vitamin K antagonist treatment.

EPVC has recommended:

- Acquired haemophilia must be promptly recognised to minimise the time the patient is at risk of bleeding and avoid major bleeding.
- In case of confirmed isolated activated Partial Thromboplastin Time (aPTT) prolongation with or without bleeding, acquired haemophilia should be considered.
- Patients with a confirmed diagnosis of acquired haemophilia should be managed and treated by specialists, clopidogrel should be discontinued and invasive procedures should be avoided.

***References*:** Egyptian Pharmaceutical Vigilance Center (EPVC), Newsletter. November 2014, Volume 5, Issue 11.

(See WHO Pharmaceuticals Newsletter No.1, 2014 for information on Risk of acquired haemophilia in the UK)

Colistin, colistimethate sodium (known as polymyxins)

Recommendations issued for safe use in patients with serious infections resistant to standard antibiotics

Europe. The EMA has reviewed the safety and effectiveness of products containing the antibiotics colistin or colistimethate sodium (known as polymyxins) and recommended changes to their product information to ensure safe use in the treatment of serious infections that are resistant to standard antibiotics.

Polymyxin-based products have been available since the 1960s, but their use quickly decreased due to the availability of antibiotics with fewer potential side effects. Due in part to this limited use, colistimethate sodium has retained activity against a number of bacteria which have become resistant to commonly used antibiotics. This has led to a resurgence in recent years in the use of polymyxins in patients with few other options. However, current experience has raised concerns that the existing product information, in particular relating to dosing and the way the medicine is handled in the body (pharmacokinetics), might need updating. The European Commission therefore requested the EMA to review the available data and make recommendations on whether the marketing authorisations for these medicines should be changed and the product information amended appropriately.

The Agency reviewed the available clinical, pharmacological and pharmacokinetic data and considered that in the interim the product information should be updated throughout the EU to reflect what was currently known.

- Doses should always be expressed in IU of colistimethate sodium. To address the differences in the way in which the strength of colistimethate sodium and colistin are expressed in the EU and in other regions such as the USA and Australia, which has led to errors in reporting in the medical literature and could potentially lead to serious medication errors, the following table has been recommended for inclusion in product information:

Colistimethate sodium(IU)	Colistimethate sodium(mg)	Colistin-base activity (CBA)(mg)
12 500	1	0.4
150 000	12	5
1 000 000	80	34
4 500 000	360	150
9 000 000	720	300

- Intravenous colistimethate sodium is indicated in adults and children including neonates for the treatment of serious infections due to aerobic Gram-negative pathogens in patients with limited treatment options. Consideration should be given to co-administration with another antibacterial agent whenever this is possible.
- Dosage should be in line with relevant treatment guidelines. Based on the limited available evidence the recommended dose in adults is 9 million IU daily in 2 or 3 divided doses as a slow intravenous infusion; in critically ill patients a loading dose of 9 million IU should be given. Doses should be reduced according to creatinine clearance in patients with renal impairment.
- In children, the suggested dose is 75,000 to 150,000 IU/kg daily, in 3 divided doses.
- Intravenous colistimethate sodium does not cross the blood-brain barrier to a significant extent. Where appropriate, adult doses of 125,000 IU for intraventricular administration and no more than this for intrathecal administration are recommended.
- Use of intravenous colistimethate sodium together with other medications that are potentially nephrotoxic or neurotoxic should be undertaken with great caution.
- When given by inhalation, colistimethate sodium solutions may be used for the management of chronic pulmonary infections due to Pseudomonas aeruginosa in adults and children with cystic fibrosis. The recommended dose in adults is 1 to 2 million IU given 2 to 3 times a day, and in children 0.5 to 1 million IU twice daily, adjusted according to the severity of the condition and the response.

A parallel review is currently underway, looking at the quality of the products and the way the potency of colistimethate sodium is measured and tested, and may result in further changes to the product information once complete.

Reference:
Press release, EMA, 24 October 2014 (*www.ema.europa.eu*)

Colobreathe® (colistimethate sodium dry powder for inhalation)

Risk of capsule breakage

UK. The MHRA reported that it has received reports of colistimethate sodium (Colobreathe®) capsules shattering when pierced by their inhaler device. The instructions for inhaler use have been revised to reduce this risk.

Colistimethate sodium dry powder for inhalation is indicated for the management of chronic *Pseudomonas aeruginosa* lung infections in patients with cystic fibrosis aged 6 years and older.

Colistimethate sodium is inhaled as a powder from a gelatine capsule using the supplied inhaler device. A piston within the inhaler pierces the capsule allowing the capsule contents to be inhaled.

To date, MHRA have received 26 reports of capsules shattering when pierced. The filter in the inhaler catches pieces of broken capsule shell more than 2 mm wide. However, smaller pieces could be swallowed or inhaled. Some reports of broken capsules have been associated with throat irritation and coughing, although there are no serious safety concerns and patients need not be alarmed if this happens.

The manufacturer has revised the instructions for inhaler use to reduce the risk of capsules breaking. These revised instructions have been included in the patient information leaflet and summary of product characteristics.

Advice for health-care professionals:

- Demonstrate the new inhaler instructions to patients. The key points are:
  - insert the capsule widest end first into the inhaler chamber.
  - pierce the capsule gradually using a two-step process
  - only pierce each capsule once
- Supervise patients taking their first dose.
- Tell patients and carers to refer to the instructions in the patient information leaflet that comes in the pack.

Reference:
Drug Safety Update, November 2014, Volume 8, issue 4, A2 MHRA, (*www.mhra.gov.uk*)

Denosumab

Risk of Osteonecrosis of the jaw and hypocalcaemia

Egypt. EPVC has informed a risk of osteonecrosis of the Jaw (ONJ) and hypocalcaemia with denosumab.

Denosumab is a human monoclonal IgG2 antibody produced in a mammalian cell line (CHO) and is used for prevention of skeletal related events (pathological fracture, radiation to bone, spinal cord compression or surgery to bone) in adults with bone metastases from solid tumors.

ONJ is a condition in which the jawbone becomes necrotic, exposed, and does not heal within 8 weeks. The etiology of ONJ is not clear, but may be associated with inhibition of bone remodeling. Known risk factors for ONJ include invasive dental procedures (e.g., tooth extraction, dental implants, oral surgery), poor oral hygiene, or other pre-existing dental disease. Other risk factors for ONJ are advanced malignancies, infections, older age, concomitant therapies (e.g., chemotherapy, corticosteroids, angiogenesis inhibitors, radiotherapy to the head and neck), smoking, and previous treatment with bisphosphonates. While on treatment, patients should avoid invasive dental procedures if possible.

EPVC has recommended:

- Before starting denosumab, a dental examination with appropriate preventive dentistry is recommended.
- Do not start denosumab in patients with an active dental or jaw condition requiring surgery, or in patients who have not recovered following oral surgery.
- Tell patients receiving denosumab to maintain good oral hygiene practices, receive routine dental check-ups, and immediately report any oral symptoms such as dental mobility, pain, or swelling during treatment with denosumab.
- Pre-existing hypocalcaemia must be corrected prior to initiating therapy with denosumab.
- Supplementation with calcium and vitamin D is required in all patients unless hypercalcaemia is present.
- Monitoring of calcium levels should be conducted:
  - prior to the initial dose of denosumab
  - within two weeks after the initial dose
  - if suspected symptoms of hypocalcaemia occur
- Consider monitoring calcium levels more frequently during therapy in patients with risk factors for hypocalcaemia (e.g. patients with severe renal impairment, creatinine clearance <30 ml/min), or if otherwise indicated based on the clinical condition of the patient.

***References*:** Egyptian Pharmaceutical Vigilance Center (EPVC), Newsletter. November 2014, Volume 5, Issue 11.

(See WHO Pharmaceuticals Newsletter No.5, 2014 for Updated recommendations on minimising the risk of osteonecrosis of the jaw and hypocalcaemia in the UK, No.3, 2013 for Severe hypocalcaemia in Australia, No.6, 2012 for Fatal cases of severe symptomatic hypocalcaemia in the UK and for Association with the risk of atypical femoral fractures in Canada and No.4, 2012 for Risk of severe symptomatic hypocalcemia, including fatal cases in Canada and for Osteonecrosis of the Jaw (ONJ) in New Zealand)

Immunoglobulins

Risk of blood clots (thrombosis)

Canada. Health Canada informed that a safety review was initiated to examine the information in the Canadian product monograph on the risk of blood clots (thrombotic events) for all non-hyperimmune immunoglobulin products (referred to as immunoglobulins for the purpose of this summary). The review was prompted by the ongoing assessment of information regarding these products and this adverse event, including data provided by manufacturers, two scientific and medical publications as well as regulatory actions by the US FDA.

The immunoglobulins are a large and diverse group of products derived from human blood and their use in clinical settings varies widely from region to region.

Based on information reviewed, it was determined that there is enough evidence for updating the information for all immunoglobulin products.

The following actions have been undertaken by Health Canada:

- The Canadian product information for all immunoglobulin products has been updated to include a Boxed Warning and an updated Warnings and Precautions section with information regarding the risk of thrombosis, by describing the type of events that may occur as well as risk factors.
- A risk communication will be issued to inform about the risk of thrombosis with immunoglobulin products.
- Monitoring of thrombosis cases for all immunoglobulin products will continue, with a

particular focus on the intramuscular and subcutaneous immunoglobulin products.

Reference:
Advisories, Warnings and Recalls, Health Canada, 9 October 2014 (*www.hc-sc.gc.ca*)

Ponatinib

Risk of blood clots and blockages in the arteries

Europe. The EMA reviewed the benefits and risks of ponatinib (Iclusig®), a medicine used for the treatment of leukaemia (cancer of the white blood cells), and recommended strengthened warnings in the product information aimed at minimising the risk of blood clots and blockages in the arteries.

Ponatinib is authorised for use in patients with chronic myeloid leukaemia (CML) and acute lymphoblastic leukaemia (ALL) who cannot take or tolerate several other medicines of the same class (known as 'tyrosine-kinase inhibitors').

The benefit-risk balance of ponatinib remains positive in all authorised indications, and the starting dose remains 45mg per day.

The product information will be updated with strengthened monitor patients for high blood pressure or signs of heart problems.

Health-care professionals should follow these recommendations:

- The cardiovascular status of the patient should be assessed before starting therapy with ponatinib, and regularly monitored during treatment.
- Treatment with ponatinib should be stopped if a complete haematologic response has not occurred by three months. Dose modifications or treatment interruption (temporary or permanent) should be considered to manage treatment toxicity.
- If a reduced dose of ponatinib is used, doctors should monitor patients for maintenance of therapeutic response.
- Any assessment relating to dose reduction should take into account a number of factors, including the patient's cardiovascular risk, side effects of therapy, and time to cytogenetic response.

Reference:
Press release, EMA, 24 October 2014 (*www.ema.europa.eu*)

(See WHO Pharmaceuticals Newsletter No.1, 2014 for Risk of serious blood clots in arteries and veins in the USA, No.1, 2014 for Risk of vascular occlusive events in the UK, No.6, 2013 for Risk of serious

rituximab and its usage in population known to bear a high potential risk of hepatitis C virus infestation.

Rituximab is a genetically engineered chimeric mouse/human monoclonal antibody representing a glycosylated immunoglobulin with human IgG1 constant regions and murine light-chain and heavy-chain variable region sequences and is used to treat diseases which are characterized by excessive numbers of B cells, overactive B cells, or dysfunctional B cells.

EPVC has recommended the following:

- Due to the High prevalence rate of HCV positive patients amongst the Egyptian population, patient should be screened for serum hepatitis C viral antibody (HCV Ab) in addition to the previously known hepatitis B virus surface antigen (HBV sAg) testing, before the initiation of treatment.
- Caution is required when rituximab is prescribed for patients with a history of recurrent or chronic infection or an underlying disease that favors the occurrence of severe infections. Patients who develop an infection after treatment with rituximab should be promptly investigated and appropriately treated.