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 documents.

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Acetaminophen

Association with risk of serious skin reactions

USA. The U.S. Food and Drug Administration (FDA) notified health-care professionals and patients that acetaminophen has been associated with a risk of rare but serious skin reactions. Acetaminophen is a common active ingredient to treat pain and reduce fever; it is included in many prescription and over-the-counter products. These skin reactions, known as Stevens-Johnson Syndrome (SJS), toxic epidermal necrolysis (TEN), and acute generalized exanthematous pustulosis (AGEP), can be fatal. These reactions can occur with first-time use of acetaminophen or at any time while it is being taken. Other drugs used to treat fever and pain/body aches (e.g., non-steroidal anti-inflammatory drugs, or NSAIDS, such as ibuprofen and naproxen) also carry the risk of causing serious skin reactions, which is already described in the warnings section of their drug labels.

This new information resulted from the Agency's review of the FDA Adverse Event Reporting System (FAERS) database and the medical literature to evaluate cases of serious skin reactions associated with acetaminophen. It is difficult to determine how frequently serious skin reactions occur with acetaminophen, due to the widespread use of the drug, differences in usage among individuals (e.g., occasional vs. long-term use), and the long period of time that the drug has been on the market; however it is likely that these events (i.e., SJS, TEN, and AGEP) occur rarely.

It is recommended that health-care professionals should be aware of this rare risk and consider acetaminophen, along with other drugs already known to have such an association, when assessing patients with potentially drug-induced skin reactions. Any patient who develops a skin rash or reaction while using acetaminophen or any other pain reliever/fever reducer should stop the drug and seek medical attention right away. Anyone who has experienced a serious skin reaction with acetaminophen should not take the drug again and should contact their health-care professional to discuss alternative pain relievers/fever reducers.

The US FDA will require that a warning be added to the labels of prescription drug products containing acetaminophen to address the risk of serious skin reactions. The US FDA will also request that manufacturers add a warning about serious skin reactions to the product labels of OTC acetaminophen drug products marketed under a new drug application and will encourage manufacturers of drug products marketed under the OTC monograph do the same.

References:
FDA Drug Safety Communication, US FDA 1 August 2013 (*www.fda.gov*).

Caffeine for apnoea of prematurity

All products to be named and prescribed as caffeine citrate

UK. The MHRA announced that the name of caffeine products supplied by Viridian Pharma Limited is being changed to caffeine citrate in order to minimise potential risk to premature newborns when prescribing or dispensing. This change brings the Viridian products in line with the naming of other products available on the UK market (ie, which are already named in the salt form as caffeine citrate). All product doses should be prescribed as caffeine citrate, taking into account the different strengths of the marketed products.

Caffeine (citrate) is authorised for treatment of apnoea of premature newborns and may be given orally or intravenously.

There is no change to the formulation of these products. The new packaging of Viridian Pharma products displaying the new name may not be immediately available. However, all packaging (current and new) has dual labelling, which clearly states the strengths of both caffeine and caffeine citrate.

Doses specified when prescribing should always be expressed as caffeine citrate because of a risk of confusion and potential for dosing errors (2 mg caffeine citrate is equivalent to 1 mg caffeine).

Health-care professionals are also advised that caffeine citrate is for use in neonatal intensive care units only, and treatment must be initiated under the supervision of a physician experienced in neonatal intensive care

Reference:
Drug Safety Update, August 2013, Volume 7, issue 1, A2 MHRA, (*www.mhra.gov.uk*).

Calcitonin medicines

Important changes to the availability and conditions of use

Canada Health Canada informed of important changes to the availability and recommended conditions of use of drugs containing calcitonin. Calcitonin is used as a nasal spray to treat osteoporosis in postmenopausal women and as an injection to treat Paget's disease and hypercalcemia.

A safety review conducted by Health Canada concluded that there is a slightly increased risk of cancer associated with the prolonged use of calcitonin products. A review of the benefits and risks of the nasal spray products found that there was not enough evidence of benefit to continue using calcitonin nasal sprays in treating osteoporosis, given the increased risk of cancer.

As a result of these reviews, calcitonin nasal spray products will no longer be authorized for sale in Canada as of October 1, 2013.

Calcitonin injectable products will continue to be authorized for sale in Canada. The benefits of these products are considered to outweigh the risks when the product is used as directed in the Product Monograph (i.e., for Paget's disease and hypercalcemia). However, the labels for calcitonin injectable products are being updated to include a new warning about this risk, and to recommend that treatment with calcitonin solution for injection be limited to the shortest possible time, using the minimum effective dose. Treatment of symptomatic Paget's disease with calcitonin medicine should be limited to patients who are unable to use other treatments.

Patients who are taking a calcitonin medicine and who have questions should speak to their health care practitioner before making any change to their treatment. There are other medications authorized in Canada for the treatment of osteoporosis, Paget's disease and hypercalcemia. Patients should speak to their pharmacist regarding the safe disposal of calcitonin nasal spray products.

(See WHO Pharmaceuticals Newsletters No.4, 2012 for intranasal formulation for osteoporosis treatment to be withdrawn; new restriction to indication for injectable use in Paget's disease in EU)

Reference:
Advisories, Warnings and Recalls, Health Canada, 31 July 2013 (*www.hc-sc.gc.ca*).

Codeine

Restrictions on use of codeine for pain relief in children

Europe. The Coordination Group for Mutual Recognition and Decentralised Procedures – Human (CMDh) endorsed by consensus a series of risk-minimisation measures to address safety concerns with codeine-containing medicines when used for the management of pain in children. Codeine is an opioid that is authorised as a painkiller in adults and children. The effect of codeine on pain is due to its conversion into morphine in the patient's body.

This follows a review of these medicines by the European Medicines Agency's Pharmacovigilance Risk Assessment Committee (PRAC), which investigated reports of serious and fatal respiratory depression in children after taking codeine for pain relief. Most of the cases occurred after surgical removal of the tonsils or adenoids for obstructive sleep apnoea (frequent interruption of breathing during sleep).

Some of the children who had suffered severe side effects had evidence of being 'ultra-rapid metabolisers' of codeine. In these patients, codeine is converted into morphine in the body at a faster rate than normal, resulting in high levels of morphine in the blood that can cause toxic effects such as respiratory depression.

The PRAC concluded that a number of risk-minimisation measures are necessary to ensure that only children for whom the benefits are greater than the risks are given the medicine for pain relief. The CMDh agreed with the PRAC's conclusions and endorsed the following recommendations:

- Codeine-containing medicines should only be used to treat acute moderate pain in children above 12 years of age, and only if it cannot be relieved by other painkillers such as paracetamol or ibuprofen, because of the risk of respiratory depression associated with codeine use.
- Codeine should not be used at all in children (aged below 18 years) who undergo surgery for the removal of the tonsils or adenoids to treat obstructive sleep apnoea, as these patients are more susceptible to respiratory problems.
- The product information of these medicines should carry a warning that children with conditions associated with breathing problems should not use codeine.

The risk of side effects with codeine may also apply to adults. Codeine should therefore not be used in people of any age who are known to be ultra-rapid metabolisers nor in breastfeeding mothers (because codeine can pass to the baby through breast milk). The product information for codeine should also include general information for healthcare professionals, patients and carers on the risk of morphine side effects with codeine, and how to recognise their symptoms.

(See WHO Pharmaceuticals Newsletters No.4, 2013 for restricted use as analgesic in children and adolescents under 18 in the UK).

Reference:
Press release, EMA, 28 June 2013 (*www.ema.europa.eu*).

Diclofenac

New measures to minimise cardiovascular risks

Europe. The CMDh endorsed by majority new safety advice for diclofenac-containing medicines that are given by means such as capsules, tablets, suppositories or injections, intended to have an effect on the whole body (known as a systemic effect). The new advice aims to minimise the risks of effects on the heart and circulation from these medicines.

This follows a recent review by PRAC, which found that the effects of systemic diclofenac on the heart and circulation are similar to those of selective COX-2 inhibitors, another group of painkillers. This applies particularly when diclofenac is used at a high dose and for long-term treatment. The PRAC therefore recommended that the same precautions already in place to minimise the risks of blood clots in the arteries with selective COX-2 inhibitors should be applied to diclofenac. The CMDh agreed with the PRAC conclusion that although the benefits of systemic diclofenac still outweigh the risks, those risks were similar to the risks with COX-2 inhibitors, and it endorsed the recommendation that similar precautions should be applied.

Diclofenac is a widely used medicine for relieving pain and inflammation, particularly in painful conditions such as arthritis. It belongs to a group of medicines called 'non-steroidal anti-inflammatory drugs' (NSAIDs).

Health-care professionals are informed that,

- Use of diclofenac is contra-indicated in patients with established congestive heart failure (New York Heart Association class II-IV), ischaemic heart disease, peripheral arterial disease or cerebrovascular disease.
- Patients with significant risk factors for cardiovascular events (e.g. hypertension, hyperlipidaemia, diabetes mellitus, smoking) should only be treated with diclofenac after careful consideration.
- As the cardiovascular risks of diclofenac may increase with dose and duration of exposure, the shortest duration possible and the lowest effective daily dose should be used. The patient's need for symptomatic relief and response to therapy should be re-evaluated periodically.
- In the light of the above, all patients receiving regular diclofenac therapy should be reviewed at the next scheduled appointment.

(See WHO Pharmaceuticals Newsletters No.4, 2013 for New contraindications and warnings after a Europe-wide review of cardiovascular safety in the UK, and No.6, 2012 for need for updated treatment advice for diclofenac in follow-on review in EU).

Reference:
Press release, EMA, 28 June 2013 (*www.ema.europa.eu*).

Ergot derivatives

New restrictions on use of medicines containing ergot derivatives

Europe. The European Medicines Agency's Committee for Medicinal Products for Human Use (CHMP) recommended restricting the use of medicines containing dihydroergocristine, dihydroergotamine, dihydroergotoxine, nicergoline or a combination of dihydroergocryptine with caffeine. These medicines should no longer be used for any of the following indications:

- symptomatic treatment of chronic pathological cognitive and neurosensorial impairment in the elderly (excluding Alzheimer's disease and other dementia);
- ancillary treatment of intermittent claudication in symptomatic peripheral arterial occlusive disease (PAOD stage II);
- ancillary treatment of Raynaud's syndrome;
- ancillary treatment of visual acuity decrease and visual field disturbances presumably of vascular origin;
- acute retinopathies of vascular origin;
- prophylaxis of migraine headache;
- orthostatic hypotension;
- symptomatic treatment of veno-lymphatic insufficiency.

This is based on a review of data showing an increased risk of fibrosis and ergotism with these medicines.

Fibrosis can be a serious, sometimes fatal disease, which is often difficult to diagnose because of delayed symptoms and may be irreversible. The CHMP noted that there is a plausible mechanism by which ergot derivatives could cause fibrosis and ergotism. Given that the evidence for these medicines' benefits in these indications was very limited, the CHMP concluded that the benefits in the concerned indications did not outweigh the risk of fibrosis and ergotism.

Health-care professionals are also advised that patients currently taking these medicines for any of the above indications should have their treatment reviewed at a

routine (non-urgent) medical appointment.

Ergot derivatives that are only indicated for these conditions will have their marketing authorisations suspended across the European Union (EU). Some ergot derivatives are approved in some EU Member States for use in other therapeutic indications, including other circulatory disorders, treatment of dementia (including Alzheimer's disease) and treatment of acute migraine. These indications were not included in the CHMP review. Therefore these products will remain authorised and may continue to be used in those indications.

(See WHO Pharmaceuticals Newsletters No.4, 2008 for new warning on fibrosis in EU).

Reference:
Press release, EMA, 28 June 2013 (*www.ema.europa.eu*).

Filgrastim and pegfilgrastim

Risk of potentially life-threatening capillary leak syndrome

UK. The Medicines and Healthcare products Regulatory Agency (MHRA) announced that capillary leak syndrome (CLS) has been reported in recipients of filgrastim, including patients undergoing chemotherapy and a healthy donor undergoing peripheral blood progenitor-cell mobilisation; it has also been reported in recipients of pegfilgrastim undergoing chemotherapy. Episodes varied in severity and frequency. CLS is characterised by: hypotension and oedema; hypoalbuminaemia; and haemoconcentration, and may be fatal unless promptly diagnosed and managed.

Filgrastim (Neupogen®) and pegfilgrastim (Neulasta®) are recombinant granulocyte colony-stimulating factors (G-CSF) used to stimulate the proliferation and differentiation of granulocytes, especially polymorphonuclear, in various forms of neutropenia induced by chemotherapy. Filgrastim is also used to help release blood stem cells from the bone marrow of healthy donors.

The postmarketing adverse reaction reports provide good evidence of a temporal and causal association between filgrastim or pegfilgrastim treatment and CLS. However, the benefits of filgrastim and pegfilgrastim continue to outweigh the risks. Healthcare professionals should note the following to help manage and minimise the risk of CLS:

Health-care professionals are advised the following:

- Closely monitor all patients and healthy donors for CLS symptoms, which commonly have rapid onset. Symptoms include: generalised body swelling; puffiness (which may be associated with less-frequent urination); difficulty breathing; abdominal swelling; and tiredness
- Give standard symptomatic treatment immediately if symptoms occur
- Advise patients and healthy donors to contact their doctor immediately if they develop CLS symptoms
- Any suspected adverse reactions to filgrastim or pegfilgrastim should be reported on a Yellow Card

Reference:
Drug Safety Update, September 2013, Volume 7, issue 2, A1 MHRA, (*www.mhra.gov.uk*).

Flupirtine-containing medicines

Restrictions in the use of oral flupirtine

Europe. The CMDh endorsed new recommendations to restrict the use of oral flupirtine medicines and suppositories. Flupirtine is a non-opioid analgesic that has been used to treat pain, such as pain associated with muscle tension, cancer pain, menstrual pain and pain following orthopaedic surgery or injuries. These medicines should now only be used for treating acute pain in adults who cannot use other painkillers, such as non-steroidal anti-inflammatory drugs (NSAIDs) and weak opioids, and treatment should not last longer than two weeks. In addition, patients' liver function should be checked after each full week of treatment and treatment should be stopped if the patient has any signs of liver problems. Flupirtine must also not be used in patients with pre-existing liver disease or alcohol abuse problems or in patients taking other medicines known to cause liver problems.

In addition to oral medicines and suppositories, this review also covered injectable flupirtine medicines which were being given as a single injection for pain following surgery. The PRAC concluded that the benefits of injectable flupirtine continue to outweigh their risks when used in this way. Doctors using the injectable flupirtine should also follow relevant advice to minimise risk to patients.

With regard to the evidence of efficacy, the review highlighted a lack of sufficient data on the benefits of flupirtine in chronic pain. In particular, there was a lack of efficacy data on the use of flupirtine for longer than eight weeks.

Based on the findings of this review, health-care professionals were advised of the following updated recommendations:

- oral flupirtine medicines and suppositories should only be used to treat adults with acute pain and only if treatment with other painkillers (such as NSAIDs and weak opioids) is contraindicated;
- the duration of treatment with flupirtine should not exceed two weeks and patients' liver function should be checked after each full week of treatment;
- treatment must be stopped in any patient with abnormal liver function tests results or symptoms of liver disease;
- flupirtine must not be used in patients with pre-existing liver disease or alcohol abuse problems or in patients taking other medicines known to cause liver problems;
- healthcare professionals should review the treatment of patients taking flupirtine taking into account the recommendations above.

Reference:
Press release, EMA, 28 June 2013 (*www.ema.europa.eu*).

the benefits of these medicines are greater than their risks, provided that adequate measures are taken to minimise the risk of allergic reactions.

Intravenous iron medicines are used when iron supplements given by mouth cannot be used or do not work. All intravenous iron medicines have a small risk of causing allergic reactions which can be life-threatening if not treated promptly. The Committee therefore concluded that measures should be put in place to ensure the early detection and effective management of allergic reactions that may occur. Iron preparations should only be given in an environment where resuscitation facilities are available, so that patients who develop an allergic reaction can be treated immediately. In addition, the CHMP considered that the current practice of first giving the patient a small test dose is not a reliable way to predict how the patient will respond when the full dose is given. A test dose is therefore no longer recommended but instead caution is warranted with every dose of intravenous iron that is given, even if previous administrations have been well tolerated.

The CHMP also considered that, during pregnancy, allergic reactions are of particular concern as they can put both the mother and unborn child at risk. Intravenous iron

Reference:
Press release, EMA, 28 June 2013 (*www.ema.europa.eu*).

Ketoconazole, oral

Potentially fatal liver injury, risk of drug interactions and adrenal gland problems

USA (1). The US FDA took several actions related to ketoconazole (Nizoral®) oral tablets, including limiting the drug's use, warning that it can cause severe liver injuries, which may potentially result in liver transplantation or death and adrenal insufficiency by decreasing the body's production of corticosteroids, and advised that it can lead to harmful drug interactions with other medications.

The US FDA approved label changes and added a new Medication Guide to address these safety issues including a strong recommendation against its use (contraindication) in patients with liver disease, and new recommendations for assessing and monitoring patients for liver toxicity. As a result, ketoconazole oral tablets should not be a first-line treatment for any fungal infection. Ketoconazole should be used for the treatment of certain fungal infections, known as endemic mycoses, only when alternative