WHO PHARMACEUTICALS NEWSLETTER

World Health Organization

prepared in collaboration with the
WHO Collaborating Centre for
International Drug Monitoring,
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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 tenth meeting of the WHO Advisory Committee on Safety of Medicinal Products (ACSoMP).

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Oral almitrine to be withdrawn by EU

Europe. The Coordination Group for Mutual Recognition and Decentralised Procedures – Human (CMDh), a medicines regulatory body representing the European Union (EU) Member States, has endorsed the recommendation by the European Medicines Agency's (EMA's) Pharmacovigilance Risk Assessment Committee (PRAC), that permission to market oral medicines containing almitrine should be withdrawn across the EU. As the PRAC recommendation was endorsed by consensus by the CMDh, it will now be implemented directly by the Member States where oral almitrine is authorised, according to an agreed timetable.

Almitrine is a stimulant of the part of the brain responsible for the breathing reflex. In the EU, it is authorised in France, Poland and Portugal to be taken orally for the treatment of chronic respiratory failure (inability of the lungs to take in oxygen and get rid of carbon dioxide properly), which is associated with hypoxaemia (lower than normal levels of oxygen in the blood). These conditions pose a particular problem in patients with lung conditions known as chronic obstructive pulmonary disease (COPD), where the airways and air sacs inside the lungs become damaged or blocked.

The safety review of oral almitrine was requested by the French medicines agency, the National Agency for the Safety of Medicine and Health Products (ANSM), because of concerns about side effects and a view that the available evidence did not support the use of the medicine in the current management of COPD.

The PRAC concluded that there is a clear association between oral almitrine treatment and potentially serious and long-lasting peripheral neuropathy (damage to the nerves in the hands and feet) and significant weight loss that further weakens patients. The PRAC noted that cases continue to be reported even after additional precautions on the use of the medicines were put in place. Furthermore, oral almitrine is no longer included as a recommended therapy in international treatment guidelines for the management of COPD. The CMDh agreed with the PRAC conclusion that the benefits of these medicines do not outweigh their risks, and adopted a final position that the marketing authorisations should be withdrawn throughout the EU.

Health-care professionals are advised the following:

- Patients being treated with oral almitrine should have their treatment reviewed at the next scheduled appointment, and appropriate alternative treatments should be considered.
- Pharmacists should refer patients presenting a new or repeat prescription to their treating physician.
- Prescribers and pharmacists will be sent a letter giving them further information on the withdrawal of oral almitrine.

Reference:
Press release, EMA, 31 May 2013 (*www.ema.europa.eu*).

Codeine

Restricted use as analgesic in children and adolescents under 18

UK. The Medicines and Healthcare products Regulatory Agency (MHRA) announced that the use of codeine for analgesia in children and adolescents under 18 has been restricted after a European safety review. The review was triggered by case reports of children who received codeine for pain control after tonsillectomy or adenoidectomy (or both) for obstructive sleep apnoea and who developed rare, but life-threatening adverse events, including death.

Codeine is converted to morphine in the liver by the CYP2D6 enzyme. There are many genetic variations of CYP2D6, which affect the extent of this conversion in individuals. Different plasma morphine concentrations in patients' blood leads not only to different levels of pain relief, but also to a variable and unpredictable risk of side effects due to morphine's action on the brain and respiratory centre.

The MHRA advised Health-care professionals that:

- Codeine should only be used to relieve acute moderate pain in children older than 12 years and only if it cannot be relieved by other painkillers such as paracetamol or ibuprofen alone
- Codeine is now contraindicated in:
  - all children age 0–18 years who undergo tonsillectomy or adenoidectomy (or both) for obstructive sleep apnoea
  - all patients of any age known to be CYP2D6 ultra-rapid metabolisers
- Codeine is not recommended for use in children whose breathing might be compromised, including those with: neuromuscular disorders; severe cardiac or respiratory conditions; upper respiratory or lung infections; multiple trauma; or extensive surgical

procedures. Morphine toxicity may be increased in these settings
- In children age 12–18 years, the maximum daily dose should not exceed 240 mg. This may be taken in divided doses up to four times a day at intervals of no less than 6 hours. It should be used at the lowest effective dose for the shortest period. Duration of treatment should be limited to 3 days and if no effective pain relief is achieved, treatment should be reviewed by a physician
- Information should be given to parents and caregivers on how to recognise the signs and symptoms of morphine toxicity, and advice should be given to stop giving the child codeine and to seek medical attention immediately if the child shows these signs or symptoms, which include: reduced levels of consciousness; somnolence; respiratory depression; 'pin-point' pupils; lack of appetite; constipation; or nausea and vomiting
- Codeine should not be used by breastfeeding mothers because it can pass to the baby through breast milk and potentially cause harm

(See WHO Pharmaceuticals Newsletters No.5, 2012 for use in certain children after tonsillectomy and/or adenoidectomy - risk of rare, but life-threatening adverse events or death in the USA).

Reference:
Drug Safety Update, June 2013, Volume 6, issue 11, S1 MHRA, (www.mhra.gov.uk).

Cyproterone and ethinylestradiol containing medicinal products

Benefits of Diane 35 and its generics outweigh risks in certain patient groups

Europe. The CMDh endorsed the recommendation of the EMA's PRAC, which concluded that the benefits of Diane 35 (cyproterone acetate 2 mg / ethinylestradiol 35 micrograms) and its generics outweigh the risks, provided that several measures are taken to minimise the risk of thromboembolism. These medicines should be used solely in the treatment of moderate to severe acne related to androgen sensitivity or hirsutism in women of reproductive age. Furthermore, Diane 35 and generics should only be used for the treatment of acne when alternative treatments, such as topical therapy and antibiotic treatment, have failed.

Since Diane 35 and its generics act as hormonal contraceptives, women should not take these medicines in combination with other hormonal contraceptives. Concomitant use of Diane 35 and its generics with another hormonal contraceptive will expose women to a higher dose of oestrogen and increase the risk of thromboembolism.

The risk of thromboembolism occurring with these medicines is low and well known. However, to minimise this risk, further measures should be implemented in addition to the updated product information. These include providing educational materials to prescribers and patients highlighting the risks of thromboembolism, for example a prescriber checklist to ensure that the risks, together with the signs and symptoms, are discussed with the patient.

The review of Diane 35 and its generics was triggered by the French medicines agency, the National Agency for the Safety of Medicine and Health Products (ANSM), following its decision to suspend Diane 35 and its generics in France within three months. The French decision followed a national review of the medicine by ANSM. This review highlighted serious thromboembolic events and extensive off-label use of these medicines as a contraceptive only.

Despite the PRAC recommendation, ANSM proceeded with the suspension of the marketing authorisation of these medicines in France. Once the European Commission has adopted its decision, all EU Member States where Diane 35 and its generics are authorised must follow it and ensure that all agreed risk-minimisation measures, including changes to the information to prescribers and patients, are implemented.

(See WHO Pharmaceuticals Newsletter for review of Diane 35 and other medicines started following the decision by the French medicines regulatory agency to suspend the drug in EU and Canada).

Reference:
Press release, EMA, 31 May 2013 (www.ema.europa.eu).

Diclofenac

New contraindications and warnings after a Europe-wide review of cardiovascular safety

UK. The Medicines and Healthcare products Regulatory Agency (MHRA) announced that available data indicate that the cardiovascular risk with diclofenac is similar to that of the selective COX-2 inhibitors and that, consistent with COX-2 inhibitors, diclofenac is now

contraindicated in those with: ischaemic heart disease; peripheral arterial disease; cerebrovascular disease; or established congestive heart failure (New York Heart Association [NYHA] classification II–IV). Health-care professionals are advised that patients with these conditions should be switched to an alternative treatment at their next routine appointment. The new treatment advice applies to systemic formulations (ie, tablets, capsules, suppositories, and injection available both on prescription and via a pharmacy, P); it does not apply to topical (ie, gel or cream) formulations of diclofenac.

It is also advised that diclofenac treatment should only be initiated after careful consideration for patients with significant risk factors for cardiovascular events (eg, hypertension, hyperlipidaemia, diabetes mellitus, smoking)

An increased risk of heart attack and stroke with some non-selective non-steroidal anti-inflammatory drugs (NSAIDs)—such as diclofenac—is well recognised, particularly with long-term use of high doses and in patients who are already at high risk. Warnings for health-care professionals and patients have been included in the product information and in the British National Formulary for some years.

The European Medicines Agency's Pharmacovigilance Risk Assessment Committee has recently recommended updates to the treatment advice for diclofenac in light of the findings of a Europe-wide review of the cardiovascular safety of NSAIDs. The review found further evidence that the arterial thrombotic risk with diclofenac is similar to that for the selective COX-2 inhibitors.

Diclofenac is available to buy in a pharmacy without a prescription at low doses (up to 75 mg/day) for short-term use (3 days) in the UK. Pharmacists are advised to take the following steps when supplying diclofenac without prescription:

- Ask questions to exclude supply for use by people with established cardiovascular disease and people with significant risk factors for cardiovascular events
- Advise patients to take diclofenac only for 3 days before seeking medical advice
- Advise patients to take only one NSAID at a time

(See WHO Pharmaceuticals Newsletters No.6, 2012 for need for updated treatment advice for diclofenac in follow-on review in EU).

Reference:
Drug Safety Update, June 2013, Volume 6, issue 11, A2 MHRA, (*www.mhra.gov.uk*).

Hydroxyethyl starch intravenous infusion

Suspension of licences in UK and new boxed warning in the US

UK (1). The Medicines and Healthcare products Regulatory Agency (MHRA) announced that the licences for all hydroxyethyl starch (HES) products have been suspended.

HES products are synthetic colloid solutions used for plasma volume expansion in a range of clinical settings. In the UK, marketed HES products are: Volulyte®; Tetraspan®; Venofundin®; and Voluven®.

The EU Pharmacovigilance Risk Assessment Committee has reviewed the balance of benefits and risks of HES products in different patient groups. The review concluded that there is a clear indication of harm when HES is used for fluid resuscitation, and no evidence of a greater benefit, compared with crystalloid solutions. The risks HES products pose to patients are considered to outweigh the benefits in all clinical settings. Although a formal EU regulatory position has not been finalised, on the advice of the Commission on Human Medicines, the licences and therefore use of HES products is being suspended in the UK.

Health-care professionals are advised that:

- There is clear evidence of harm from increased renal dysfunction and mortality associated with the use of HES, and overall the risks outweigh the benefits
- There is no evidence that infusion solutions containing HES for plasma volume expansion provide additional clinically relevant benefit to patients compared with crystalloids in any indication
- HES should not be used for plasma volume expansion. An alternative resuscitation fluid should be selected according to clinical guidelines
- A recall of all remaining HES stock has been issued

USA (2). The U.S. Food and Drug Administration (FDA) concluded that Hydroxyethyl starch (HES) solutions should not be used in critically ill adult patients, including patients with sepsis and those admitted to the ICU, and a Boxed Warning to include the risk of mortality and severe renal injury is warranted. In addition, The US FDA reviewed a meta-analysis of studies conducted in patients undergoing open heart surgery in association with cardiopulmonary bypass and determined that an additional warning about excessive bleeding is needed in the Warnings and Precautions Section of the package insert.

HES solutions are used for the treatment of hypovolemia when plasma volume expansion is desired. Recent

data have associated the use of these products with an increased risk of severe adverse events when used in certain patient populations.

In the US, recommendations for health-care professionals include the following:

- Do not use HES solutions in critically ill adult patients including those with sepsis, and those admitted to the ICU.
- Avoid use in patients with pre-existing renal dysfunction.
- Discontinue use of HES at the first sign of renal injury.
- Need for renal replacement therapy has been reported up to 90 days after HES administration. Continue to monitor renal function for at least 90 days in all patients.
- Avoid use in patients undergoing open heart surgery in association with cardiopulmonary bypass due to excess bleeding.
- Discontinue use of HES at the first sign of coagulopathy.

Reference:

(1) Drug Safety Update, June 2013, Volume 6, issue 11, A1 MHRA, (www.mhra.gov.uk).
(2) FDA Drug Safety Communication, US FDA 24 June 2013 (www.fda.gov).

Ketoconazole

Risk of potentially fatal liver toxicity

Canada. The manufacturers of ketoconazole, in collaboration with Health Canada, have revised to the Product Monograph (PM) regarding the risk of potentially fatal liver toxicity. Ketoconazole has been associated with rare cases of serious hepatotoxicity including liver failure and death. This risk was also observed in patients with no pre-existing liver disease and no serious underlying medical conditions. Hepatotoxicity and death have been reported to occur at recommended doses and with treatment courses longer than 10 days.

The Warnings' sections of the PM was updated to include the following additional instructions:

- Ketoconazole tablets are indicated for the treatment of serious or life threatening systemic fungal infections and should not be considered for mild to moderate infections.
- Oral ketoconazole has been associated with hepatic toxicity, including cases with fatal outcomes.
- Liver function tests should be performed in all patients before starting treatment, at week 2 and 4, and monthly thereafter.
- Treatment should be stopped if liver parameters are elevated (> 3 times the normal limit) or if patients develop clinical signs or symptoms consistent with liver disease such as anorexia, nausea, vomiting, jaundice, fatigue, abdominal pain, dark urine, or pale stools.

Health-care practitioners are advised to consider the risk of fatal liver toxicity with ketoconazole when prescribing antifungal treatment for patients who are already at risk for liver toxicity. It is also advised that patients using ketoconazole concurrently with potentially hepatotoxic drugs should be carefully monitored, especially in those expected to be on prolonged therapy or at risk for hepatotoxicity.

Reference:

Advisories, Warnings and Recalls, Health Canada, 19 June 2013 (www.hc-sc.gc.ca).

Olmesartan medoxomil

Label changes to include sprue-like enteropathy

USA. The US FDA warned that olmesartan medoxomil (Benicar®, Benicar HCT®, Azor®, Tribenzor®, and generics) can cause intestinal problems known as sprue-like enteropathy. Symptoms of sprue-like enteropathy include severe, chronic diarrhea with substantial weight loss. FDA has approved changes to the labels of these drugs to include this concern. Sprue-like enteropathy has not been detected with angiotensin II receptor blockers (ARB) other than olmesartan.

Olmesartan medoxomil is ARB approved for the treatment of high blood pressure, alone or with other antihypertensive agents.

Health-care professionals are recommended to tell patients to contact them if they develop severe, chronic diarrhea with substantial weight loss while taking an olmesartan-containing product, even if it takes months to years for symptoms to develop. Patients should contact their health-care professional right away if they take an olmesartan-containing product and experience severe diarrhea, diarrhea that does not go away, or significant weight loss.

References:

FDA Drug Safety Communication, US FDA 3 July 2013 (www.fda.gov).

Strontium ranelate

Recommendation to restrict the use and further review started

Europe. The CHMP recommended a restriction in the use of strontium ranelate (Protelos® and Osseor®), following an assessment of data showing an increased risk of serious heart problems. The CHMP recommended that the drug should only be used to treat severe osteoporosis in postmenopausal women at high risk of fracture and severe osteoporosis in men at

increased risk of fracture. Additional measures, including restrictions in patients with heart or circulatory problems, were also recommended to minimise the heart risks of these medicines.

The CHMP recommendation is based on the advice of the PRAC, which evaluated strontium ranelate as part of a routine benefit-risk assessment. During the assessment, data from clinical studies in post-menopausal women were evaluated, showing a higher risk of heart attack with the drug than with placebo, with no observed increase in mortality risk. Given the other serious risks (blood clots and rare serious skin reactions) previously identified with the medicine, the PRAC concluded that certain restrictions in the use of the medicine should be in place for the benefit-risk balance to remain favourable and that a further in-depth evaluation of the benefits and risks of the medicine was needed.

The CHMP agreed with the PRAC's recommendations and this opinion will be sent to the European Commission for a legally binding decision. A further wide-ranging evaluation of the benefits and risks of strontium ranelate will now be conducted by PRAC and CHMP. In the meantime, the current recommendations are intended to minimise the risk of serious heart problems.

cerebrovascular disease, or in patients with uncontrolled hypertension.
- Treatment with strontium ranelate should only be started by a physician experienced in the treatment of osteoporosis.
- Physicians should base their decisions to prescribe strontium ranelate on an assessment of the individual patient's risks. The patient's risk of developing cardiovascular disease should be evaluated before and at regular intervals during treatment.
- Treatment should be stopped if the patient develops ischaemic heart disease, peripheral arterial disease or cerebrovascular disease or if hypertension becomes uncontrolled.

(See WHO Pharmaceuticals Newsletter No. 3, 2013 for risk of serious cardiac disorders in UK).

Reference:
Press release, EMA, 26 April 2013 (*www.ema.europa.eu*).

Retigabine

Restricted use is recommended due to risk of retinal pigmentation

Europe. The CHMP recommended restricting the use of the anti-epileptic medicine retigabine (Trobalt®) only to those patients for whom other anti-epileptic

be reviewed at a routine (non-urgent) appointment. The balance of benefits and risks should be re-evaluated, and patients should be informed of the latest safety information. The CHMP also recommended that a comprehensive eye examination should be performed at the start of treatment (for new patients) and at least every six months during treatment. If retinal pigment or vision changes are detected, treatment with the drug should only be continued after a careful re-assessment of the balance of benefits and risks.

In its assessment, the CHMP took into account not only the importance of retinal pigmentation, as it could possibly result in impaired vision, but also considered that uncontrolled epilepsy is a serious condition which may be life-threatening if left untreated. The CHMP therefore concluded that the drug remains a valuable alternative option for patients whose epilepsy cannot be controlled by other medicines.

Reference:
Press release, EMA, 31 May 2013 (*www.ema.europa.eu*).

Varenicline tartrate and bupropion hydrochloride

Revision to the Product Monograph of non-