Safety and efficacy issues

Combined hormonal contraceptives and venous thromboembolism
European Union – The European Medicines Agency’s Committee for Medicinal Products for Human Use (CHMP) has completed its review of risks associated with combined hormonal contraceptives (CHCs), and has concluded that the benefits of CHCs in preventing unwanted pregnancies continue to outweigh their risks.

The product information of CHCs will be updated to help women make informed decisions about their choice of contraception. When prescribing a CHC healthcare professionals should consider the individual woman’s current risk factors. CHCs are contraindicated if a woman has one serious risk factor or multiple risk factors for blood clots.


Clobazam: serious skin reactions
United States of America – The Food and Drug Administration (FDA) is warning the public that clobazam (Onfi®), a benzodiazepine medication used with other medicines to treat seizures in a severe form of epilepsy, can cause rare but serious skin reactions that can result in permanent harm and death.

FDA identified clobazam as the likely cause in a number of reports of Stevens-Johnson syndrome and toxic epidermal necrolysis. The risk appeared to be greatest during the first 8 weeks after starting or re-starting clobazam treatment.

Patients taking clobazam should seek immediate medical attention if they develop a rash, blistering or peeling of the skin, sores in the mouth, or hives. Health care professionals should discontinue clobazam and consider an alternate therapy at the first sign of rash, unless it is clearly not drug-related. Patients should not stop taking clobazam without consulting their health care professionals, as sudden withdrawal can cause serious problems such as seizures, hallucinations, shaking, nervousness, and stomach or muscle cramps.

Reference: FDA Drug Safety Communication, 3 December 2013

Amiodarone: pulmonary toxicity
New Zealand – MedSafe has informed health care professionals of pulmonary toxicity associated with amiodarone, used to treat tachyarrhythmias. Pulmonary toxicity is estimated to occur in approximately 5% of patients taking amiodarone. It can rarely present as acute respiratory distress – for example after recent surgery – with a mortality of up to 50%. Chronic symptoms are more frequent and have been associated with a mortality of up to 10% in some studies.

Early recognition is vital. All patients receiving amiodarone should be monitored for the development of pulmonary toxicity and other adverse effects; MedSafe has recommended a range of screening measures.

Pulmonary toxicity should be suspected in all patients with new or worsening symptoms whilst taking amiodarone. Amiodarone should be stopped in all suspected cases. Corticosteroids may be considered as a treatment option. Due to
amiodarone’s long half-life symptoms may initially worsen or be slow to resolve. Slow withdrawal of the corticosteroids over at least two to six months is recommended to prevent rebound pulmonary toxicity.


Methylphenidate: rare risk of long-lasting erections in males
United States of America – The Food and Drug Administration (FDA) is warning that methylphenidate products, a medicine used to treat attention deficit hyperactivity disorder (ADHD), may in rare instances cause prolonged and sometimes painful erections known as priapism. If not treated immediately, priapism can lead to permanent damage to the penis.

Priapism may be more likely to occur with the use of immediate-release methylphenidate, which has a shorter half-life. The risk with alternative treatments such as atomoxetine and amphetamine is unclear.

Male patients and their caregivers should be taught the signs and symptoms of priapism and the importance of seeking immediate medical treatment if erections lasting longer than four hours occur.


Glibenclamide: risk of hypoglycaemia in elderly and renal-impaired patients
Singapore – The Health Science Authority (HSA) had conducted a benefit-risk assessment of glibenclamide and advises against its use in patients over 60 years of age and those with impaired renal function, as these patients are at risk of developing severe, long-lasting hypoglycaemia.

In 2012, the World Health Organisation (WHO) had recommended to avoid using glibenclamide in patients older than 60 years of age. Similar recommendations were made by the US Kidney Disease Outcomes Quality Initiative (KDOQI) in 2012 and the Canadian Diabetes Association in 2013.


Subcutaneous epoetin alfa: contraindicated in Singapore in chronic kidney disease patients
Singapore – Further to local reports of antibody-mediated cases of pure red cell aplasia – a decline of red blood cells produced by the bone marrow – in patients with chronic kidney disease, the Health Sciences Authority (HSA) advises that subcutaneous (SC) epoetin alfa (Eprex®) is contraindicated in Singapore in these patients. Although a comprehensive review could not determine the root causes (such as storage/handling issues and quality/manufacturing issues), HSA considers that the totality of information on these serious and potentially life-threatening adverse events warrants a contraindication.


Acipimox: only to be used as additional or alternative treatment
European Union – The Co-ordination Group for Mutual Recognition and Decentralised Procedures - Human (CMDh) – a body representing EU Member States – has confirmed that acipimox, a medicine to treat high triglyceride levels, should be used across the European Union only when diet, exercise, and treatment with other medicines are not adequate.
The benefit-risk balance of acipimox was reviewed as a result of outcomes of a study on nicotinic acid, a related medicine, in combination with laropiprant. Findings from that study were used to expand the warnings in the acipimox product information on a possible increased risk of painful muscle damage when acipimox is used together with a statin.


**Estradiol-containing creams: new restrictions**

European Union – The European Medicines Agency’s Committee for Medicinal Products for Human Use (CHMP) advises that Linoladiol N and Linoladiol HN, two high-strength estradiol-containing creams used in postmenopausal women, may continue to be used with certain restrictions. The estradiol being absorbed from the creams into the body can cause risks similar to those in systemic hormone replacement therapy, including venous thromboembolism, stroke and endometrial cancer.

Linoladiol N may continue to be used to treat vaginal atrophy when at least one topical, lower-dose oestrogen treatment has failed. The use of Linoladiol HN, which also contains a weak corticosteroid, should be limited to treatment of mild, inflammatory skin diseases of the external genital area. Both creams should be used for no longer than four weeks at a time.


**Clopidogrel: rare reports of acquired haemophilia**

United Kingdom – The Medicines and Healthcare Products Regulatory Agency MHRA draws attention to reports of acquired haemophilia received in association with clopidogrel. This very rare but serious condition may be missed due to the established risk of bleeding associated with clopidogrel treatment.

Although these events are very rare (12 cases reported worldwide to the marketing authorization holder whereas more than 153 million patients use the medicine), healthcare professionals should be aware of this serious and possibly life-threatening risk. Prompt diagnosis is required to minimise the risks of bleeding. A possible sign of acquired haemophilia is an isolated prolonged activated partial thromboplastin time (aPTT). Patients with confirmed acquired haemophilia should be managed by specialists, and clopidogrel should be discontinued. Invasive procedures should be avoided.

**Reference:** MHRA. Drug Safety Update 7 (5), December 2013: A2.

**Sodium phosphate products in high doses: severe dehydration**

United States of America – The Food and Drug Administration (FDA) is warning that using more than one dose in 24 hours of oral or rectal sodium phosphate products can cause severe dehydration and electrolyte abnormalities associated with serious complications such as acute kidney injury and arrhythmias. Sodium phosphate over-the-counter (OTC) products are used to treat constipation.

Nearly half of the adult cases and 3% of the pediatric cases reviewed by FDA had a fatal outcome. Life-threatening effects occurred in more than two-thirds of affected adults and in all of the affected children, with acute deterioration in respiratory status, mental status and heart function. Most cases involved older adults and children younger than 5 years.
Safety and efficacy issues

FDA reminds consumers and health care professionals to always use these products as recommended on the label, and not to exceed the labeled dose. The oral products should not be given to children 5 years and younger without discussing with a health care professional. The rectal form should never be given to children under 2 years.


Emergency contraceptives – high bodyweight may reduce effectiveness

European Union – New data suggest that a high bodyweight could impair the effectiveness of emergency contraceptives in preventing an unintended pregnancy following unprotected sexual intercourse or contraceptive failure. The European Medicines Agency (EMA) has initiated a review by its Committee for Medicinal Products for Human Use (CHMP) to assess whether any changes should be made to the product information for emergency contraceptive medicines containing levonorgestrel or ulipristal acetate.

Emergency contraceptives containing levonorgestrel can be used up to 72 hours after unprotected sexual intercourse or contraceptive failure while ulipristal acetate can be used up to 120 hours. Levonorgestrel-containing emergency contraceptives are available without a prescription in certain European countries. Ulipristal acetate can only be obtained with a prescription.


Testosterone: possible risk of stroke and heart attack

United States of America – Outcomes of two recent studies prompted the Food and Drug Administration (FDA) to reassess the risk of stroke, heart attack and death associated with testosterone products. These products are FDA-approved only for use in men who lack or have low testosterone levels due to a medical reason such as genetic problems or chemotherapy. Approved formulations include the topical gel, transdermal patch, buccal system (applied to upper gum or inner cheek), and injection.

Awaiting the outcomes of the FDA review, health care professionals should consider the risks and benefits of FDA-approved testosterone treatment, and should report side effects to the FDA MedWatch program.


Lithium: hypercalcaemia and hyperparathyroidism

Canada – Health Canada has reviewed available evidence and has determined that lithium therapy can cause hypercalcaemia, which may or may not be accompanied with hyperparathyroidism. However, the benefits of lithium in the treatment of manic episodes of manic-depressive illness continue to outweigh the known risks. The authority advises health professionals to consider calcium and parathormone blood levels before and during treatment, and to report any cases of serious hypercalcaemia and hyperparathyroidism or other serious or unexpected adverse events to Health Canada.

Saxagliptin: possible risk of heart failure
United States of America – The Food and Drug Administration (FDA) has requested clinical trial data from the manufacturer of saxagliptin (Onglyza®, Kombiglyze XR®) to investigate a possible association between use of the type 2 diabetes medicine and heart failure. A preliminary study did not find increased rates of death or other major cardiovascular risks. FDA urges health care professionals and patients to report side effects involving saxagliptin products to the FDA MedWatch programme.

Strontium ranelate: further restrictions due to cardiovascular risks
European Union – The Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency has concluded its review of strontium ranelate (Proteos®/Osseor®) and has recommended further restricting its use to patients with severe osteoporosis who have a high risk of fracture and cannot be treated with other approved medicines. 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 must not use the medicine.

The Pharmacovigilance Risk Assessment Committee (PRAC) had recommended to suspend the medicine. The CHMP determined that for patients who have no alternative treatment it has benefits in preventing fractures, and that regular screening and monitoring every 6 to 12 months to exclude cardiovascular disease will sufficiently reduce the risk. Educational material will be provided to prescribers to ensure that only the appropriate patients are treated with the medicine. The marketing authorization holder is required to conduct further research to demonstrate the effectiveness of the new measures.

Methysergide-containing medicines: new restrictions
European Union – The European Medicines Agency (EMA) has recommended restricting the use of methysergide, an ergot alkaloid medicine, due to concerns over its association with fibrosis raised by the French medicines agency ANSM in May 2012. Fibrosis is a condition in which scar tissue accumulates in the body’s organs.

Methysergide-containing medicines are now only to be used for preventing severe intractable migraines and cluster headaches when alternative treatment has failed. It is no longer recommended to treat diarrhoea caused by carcinoid disease. Treatment should be started and supervised by an experienced specialist. Patients should be screened for fibrosis at the start of treatment and every 6 months thereafter to prevent severe and potentially life-threatening damage to organs.