New MHRA drug safety advice: May to July 2013

The MHRA and CHM publish the monthly newsletter Drug Safety Update highlighting important information and advice to support the safer use of medicines. To subscribe to Drug Safety Updates from the MHRA, please visit this link to register.

The MHRA has provided the following synopsis of the key drug safety issues from the May, June and July 2013 Drug Safety Updates:

**Thalidomide: risk of second primary malignancies**¹
Patients treated with thalidomide have an increased risk of haematological second primary malignancies (acute myeloid leukaemia and myelodysplastic syndromes). Healthcare professionals should consider this risk during the decision to treat with thalidomide, and should monitor patients for the occurrence of these conditions.

**Tolvaptan (Samsca▼): risk of liver injury—liver-function testing recommended in patients with symptoms that may indicate liver injury**²
Tolvaptan (Samsca▼) is a treatment for adults with hyponatraemia secondary to inappropriate antidiuretic hormone secretion.

Drug-induced liver injury has been observed in clinical trials investigating potential use in patients with autosomal dominant polycystic kidney disease (an unlicensed indication) at higher doses than those for the approved indication and in long-term use.

Liver-function tests should be done in patients taking tolvaptan who report signs or symptoms that suggest liver injury. Treatment with tolvaptan should be stopped during investigations into the probable cause of liver injury and patients treated with alternative appropriate treatment.

**Cyproterone acetate with ethinyloestradiol (co-cyprindiol): balance of benefits and risks remains positive—updated prescribing advice provided**³
Following a Europe-wide review of cyproterone acetate with ethinyloestradiol (co-cyprindiol), the balance of benefits and risks of Dianette (brand leader) and its generics remains positive. To further improve the benefit-risk balance some important changes have been made to clarify the indication—these are discussed in the article. Although the indications for co-cyprindiol relate to androgen-sensitive skin conditions and hirsuitism, the medicine also provides effective contraception for women who require it. Use of additional hormonal...
contraception with co-cyprindol is therefore contraindicated. The risk of venous thromboembolism is rare but healthcare professionals and patients should remain vigilant for signs and symptoms of this important side effect.

**Diclofenac: new contraindications and warnings after a Europe-wide review of cardiovascular safety**

Available data indicate that the cardiovascular risk with diclofenac is similar to that of the selective COX-2 inhibitors. Consistent with COX-2 inhibitors, diclofenac is now contraindicated in those with: ischaemic heart disease; peripheral arterial disease; cerebrovascular disease; established congestive heart failure (New York Heart Association classification II–IV). The [new treatment advice](#) applies to systemic formulations (i.e. tablets, capsules, suppositories, and injection available both on prescription and via a pharmacy); it does not apply to topical (i.e. gel or cream) formulations of diclofenac.

**Hydroxyethyl starch intravenous infusion: suspension of licences**

Results from large randomised clinical trials (2 of sepsis and 1 of critically ill patients) have reported an increased risk of renal dysfunction and mortality in patients who received hydroxyethyl starch (HES) compared with crystalloids. The risks of HES products for plasma volume expansion outweigh the benefits in all patient groups and clinical settings. The licences for all HES products have been suspended.

**Oral retinoids: pregnancy prevention—reminder of measures to minimise teratogenic risk**

The risk of foetal malformation with oral retinoids is extremely high, even when used at a low dose or for a short time during pregnancy. All oral retinoids have an associated Pregnancy Prevention Programme, which is supported by educational material for prescribers, pharmacists, and patients. Women of child-bearing potential should have pregnancy excluded before starting treatment. While taking these medicines, 1—or preferably 2—different forms of contraception must be consistently used.

**Codeine for analgesia: restricted use in children because of reports of morphine toxicity**

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. Furthermore, a significant risk of serious and life-threatening adverse reactions has been identified in children with obstructive sleep apnoea who received codeine after tonsillectomy or adenoidectomy (or both). Codeine is now contraindicated in all children younger than 18 years who undergo these procedures for obstructive sleep apnoea.

**Retigabine (Trobalt▼): indication restricted to last-line use, and new monitoring requirements after reports of pigment changes in ocular tissue, skin, lips, or nails**

Retigabine (Trobalt▼) should now only be used as an adjunctive treatment for drug-resistant partial onset seizures with or without secondary generalisation in patients age 18 years or older with epilepsy, where other appropriate drug combinations have proved inadequate or have not been tolerated.

Pigment changes (i.e. discoloration) of ocular tissue—including the retina—have been reported in long-term clinical studies of retigabine and a compassionate use programme. These studies also observed blue-grey discoloration of the nails, lips, or skin. These reports are considered to be very common (ie, occurring in ≥1/10 patients) after prolonged retigabine treatment. Patients who are currently receiving retigabine treatment should be reviewed at a routine appointment. Comprehensive ophthalmic examination should be done at the start of treatment and at least every 6 months thereafter during treatment. Treatment should only
continue after a careful reassessment of the balance of benefits and risks if pigment changes are detected

**Ondansetron for intravenous use: dose-dependent QT interval prolongation—new posology**

There is new guidance for intravenous use of ondansetron in relation to repeat dosing for all adults; dosing for prevention of chemotherapy-induced nausea and vomiting in patients age 75 years or older; and dilution and administration for patients age 65 years or older.

**Study sponsorship**

The process used to produce Drug Safety Update is NICE accredited.

**References**


**About this Medicines Evidence Commentary**

Medicines Evidence Commentaries form part of NICE’s Medicines Awareness Service and help contextualise important new evidence, highlighting areas that could signal a change in clinical practice. They do not constitute formal NICE guidance. The opinions of contributors do not necessarily reflect the views of NICE.

Visit Evidence Search

Copyright © 2013 National Institute for Health and Care Excellence. All Rights Reserved.