Drug Safety Update

Latest advice for medicines users

The monthly newsletter from the **MHRA** and its independent advisor the **Commission on Human Medicines**

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Contents

The MHRA is the government agency which is responsible for ensuring that medicines and medical devices work, and are acceptably safe.

The Commission on Human Medicines gives independent advice to ministers about the safety, quality, and efficacy of medicines. The Commission is supported in its work by Expert Advisory Groups that cover various therapeutic areas of medicine.

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This month, we start with news of about suspension of licences for hydroxyethyl starch (HES) products. Results from large randomised clinical trials (two of sepsis and one of critically ill patients) have reported an increased risk of renal dysfunction and mortality in patients who received HES compared with crystalloids. The risks of HES products outweigh the benefits in all patient groups and clinical settings and should not be used for plasma volume expansion (see article A1).

Also this month, we have an important update regarding the non-selective non-steroidal anti-inflammatory drug diclofenac. 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; and established congestive heart failure (New York Heart Association [NYHA] classification II–IV). Further information and advice is given in article A2. Moreover, we also have important information this month about the analgesic codeine and its use in children—see article S1.

Two articles this month are of interest to those who are involved in the care of people with severe skin conditions. Firstly, to further improve the benefit-risk balance of cyproterone acetate with ethinylestradiol (co-cyprindiol), some important changes have been made to clarify the indication. It should be used in women of reproductive age for the treatment of: skin conditions related to androgen sensitivity, such as severe acne with or without seborrhoea; or hirsutism. Furthermore, use of an additional hormonal contraceptive with co-cyprindiol is now contraindicated (see article A3). Secondly, we would like to remind healthcare professionals about the pregnancy-prevention measures in place during treatment with oral retinoids, which are potent teratogens (article H1).

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Drug safety advice

A1 Hydroxyethyl starch intravenous infusion: suspension of licences

Results from large randomised clinical trials have reported an increased risk of renal dysfunction and mortality in critically ill or septic 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

Hydroxyethyl starch (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.

Large randomised clinical trials have reported an increased risk of renal dysfunction and mortality over a 90-day follow-up in patients who received HES compared with crystalloids. Increased risk of renal dysfunction has been shown in trials of patients with sepsis[1,2] and in a large trial of critically ill patients, including a subgroup with sepsis.[3] Increased mortality at 90 days was also shown in the trials of patients with sepsis.[1,2]

The most accurate estimate of the magnitude of these risks is from meta-analyses of published data. A meta-analysis published in *JAMA* reported an increased relative risk of renal failure of 1·27 (95%CI 1·09–1·47) for HES compared with crystalloid.[4] A Cochrane review that included 25 studies with mortality data reported an increased relative mortality risk of 1·10 (95%CI 1·02–1·19) for HES compared with crystalloid.[5]

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.

Advice for healthcare professionals:

- 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

1 Brunkhorst F, et al. *N Engl J Med* 2008; **358:** 125–39.
2 Perner A, et al. *N Engl J Med* 2012; **367:** 124–34.
3 Myburgh J, et al. *N Engl J Med* 2012; **367:** 1901–11.
4 Zarychanski R, et al. *JAMA* 2013; **309:** 678-88.
5 Perel P, et al. *Cochrane Database Syst Rev* 2013; **2:** CD000567.

See guidelines from the Faculty of Intensive Care Medicine: http://www.ficm.ac.uk/news-events/risk-benefit-hes-solutions-questioned-ema

See recall details: http://www.mhra.gov.uk/Publications/Safetywarnings/DrugAlerts/CON287025

Further information from the European Medicines Agency: http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2013/06/news_detail_001814.jsp&mid=WC0b01ac058004d5c1

Article citation: Drug Safety Update June 2013 vol 6, issue 11: A1.

A2 **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; or established congestive heart failure (New York Heart Association [NYHA] classification II–IV). 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

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 healthcare 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.

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.

A recently published meta-analysis[1] of clinical trial data provides further evidence that the arterial thrombotic risk with diclofenac is similar to that of COX-2 inhibitors. This analysis found that of 1000 patients allocated to diclofenac for a year, three more had major vascular events, compared with placebo.

1 Coxib and traditional NSAID Trialists' (CNT) Collaboration. *Lancet* published online May 20, 2013: http://dx.doi.org/10.1016/S0140-6736(13)60900-9

Advice for healthcare professionals:

New advice for diclofenac

- Diclofenac is now contraindicated in patients with established:
  - ischaemic heart disease
  - peripheral arterial disease
  - cerebrovascular disease
  - congestive heart failure (New York Heart Association [NYHA] classification II–IV)

  Patients with these conditions should be switched to an alternative treatment at their next routine appointment

- Diclofenac treatment should only be initiated after careful consideration for patients with significant risk factors for cardiovascular events (eg, hypertension, hyperlipidaemia, diabetes mellitus, smoking)

Reminder of existing advice for all NSAIDs

- The decision to prescribe an NSAID should be based on an assessment of a patient's individual risk factors, including any history of cardiovascular and gastrointestinal illness

- Naproxen and low-dose ibuprofen are considered to have the most favourable thrombotic cardiovascular safety profiles of all non-selective NSAIDs

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See http://cks.nice.org.uk/nsaids-prescribing-issues#!scenariorecommendation

Further information:
New advice:
European Medicines Agency:
http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2013/06/news_detail_001816.jsp&mid=WC0b01ac058004d5c1

Reminder of existing advice:

European Medicines Agency report, Oct 2012: http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000316.jsp&mid=WC0b01ac0580225ca9#section5

Previous NSAID advice from Drug Safety Update (Oct 2012 http://www.mhra.gov.uk/Safetyinformation/DrugSafetyUpdate/CON199570, Feb 2009 http://www.mhra.gov.uk/Safetyinformation/DrugSafetyUpdate/CON088130, and Dec 2007 http://www.mhra.gov.uk/Safetyinformation/DrugSafetyUpdate/CON084694)

General NSAID advice:

MHRA website http://www.mhra.gov.uk/Safetyinformation/Generalsafetyinformationandadvice/Product-specificinformationandadvice/Product-specificinformationandadvice-A-F/CardiovascularsafetyofCOX-2inhibitorsandnon-selectiveNSAIDs/index.htm

British National Formulary http://www.bnf.org/bnf/search.htm?q=diclofenac

- The lowest effective dose should be used for the shortest duration necessary to control symptoms. A patient's need for symptomatic relief and response to treatment should be re-evaluated periodically

Additional advice for pharmacists:

Non-prescription availability of diclofenac

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). Pharmacists are asked 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

This information will be circulated via the NHS Central Alerting System (https://www.cas.dh.gov.uk) in early July.

Article citation: Drug Safety Update June 2013 vol 6, issue 11: A2.

A3 **Cyproterone acetate with ethinyloestradiol (co-cyprindiol)—balance of benefits and risks remains positive; updated prescribing advice is provided**

Following a Europe-wide review of cyproterone acetate with ethinylestradiol (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 below. 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-cyprindiol 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

Cyproterone with ethinylestradiol (co-cyprindiol, brand leader Dianette) is licensed as a second-line treatment for women with severe acne or moderately severe hirsutism. A review of the benefits and risks of co-cyprindiol was initiated in January 2013 following concerns in France about the risk of venous thromboembolism (VTE) and off-label use as a contraceptive. The review has concluded that the balance of benefits and risks of co-cyprindiol remains positive; however, some important changes to product information for prescribers and women have been made to further improve this balance.

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New information wording

Indication for use

The review considered the available data on the safety and efficacy of co-cyprindiol and concluded that it should be used in women of reproductive age for the treatment of:

- skin conditions related to androgen sensitivity, such as severe acne with or without seborrhoea
- hirsutism

Co-cyprindiol should only be used when treatment with topical therapy or systemic antibiotics has failed.

Contraceptive action

Co-cyprindiol provides effective contraception in women who require it to treat androgen-sensitive conditions, but it should not be used solely as a contraceptive.

Review of postmarketing data for adverse drug reactions has suggested that some women are using Dianette as well as a combined hormonal contraceptive. This exposes them to twice the dose of oestrogen and substantially increases their risk of VTE. Use of an additional hormonal contraceptive with co-cyprindiol **is therefore contraindicated.**

Rare risk of VTE

The risk of VTE with co-cyprindiol is rare and similar to that associated with the hormonal contraceptive pills. The available observational data have limitations, but taken together their findings provide sufficient evidence that co-cyprindiol has a 1.5–2 times statistically significant increase in VTE risk (deep vein thrombosis, DVT, or pulmonary embolism, PE) compared with levonorgestrel-containing pills. Although more limited, the available evidence also suggests that the VTE risk with Dianette is likely to be similar to that with contraceptives that contain desogestrel, gestodene, or drospirenone.

Duration of treatment

See http://www.mhra.gov.uk/Safetyinformation/DrugSafetyUpdate/CON084884

In 2008 we published updated advice on the recommended duration of use of co-cyprindiol. The recent review has confirmed that acne is a chronic condition that requires at least 3 months of treatment with Dianette to relieve symptoms, and that prolonged treatment might be needed. The need to continue treatment should be **evaluated periodically** by the treating physician.

Advice for healthcare professionals:

- The benefits of co-cyprindiol outweigh the risks in women of reproductive age for the treatment of:
  - skin conditions related to androgen sensitivity (eg, severe acne with or without seborrhoea)
  - hirsutism
- Co-cyprindiol provides effective contraception in these women. An additional hormonal contraceptive should not be used in combination with co-cyprindiol
- The need to continue treatment should be evaluated periodically by the treating physician
- The risk of VTE is rare but this remains an important side effect, and healthcare professionals should themselves be vigilant for signs and counsel patients to remain vigilant for signs and symptoms. These include:

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Further information

European Medicines Agency: http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2013/05/news_detail_001801.jsp&mid=WC0b01ac058004d5c1]

BNF section 13.6.2 Oral preparations for acne http://www.bnf.org/bnf/search.htm?q=dianette

  - DVT—unusual leg pain (usually in the calf), which may be accompanied by tenderness or swelling in the leg; increased warmth, redness, or discolouration of skin
  - PE—sudden sharp chest pains (which may increase with breathing in); shortness of breath (which can come on suddenly or gradually); sudden coughing for no apparent reason; severe light-headedness, dizziness or fainting

- Remember that suspected adverse reactions to co-cyprindiol should be reported to us on a Yellow Card (www.mhra.gov.uk/yellowcard)

Article citation: Drug Safety Update June 2013 vol6, issue 11: A3.

Hot topic

H1 **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 (PPP), 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, one—or preferably two—different forms of contraception must be consistently used

Oral retinoids are used for severe skin conditions that are resistant to other therapies.

- Isotretinoin (brand leader Roaccutane) is used to treat severe acne
- Alitretinoin (Toctino) is indicated for adults with severe chronic hand eczema
- Acitretin (Neotigason) is used for: severe, extensive, resistant psoriasis; palmo-plantar pustular psoriasis; congenital ichthyosis; and Darier's disease (keratosis follicularis)

Oral retinoids can only be prescribed within a team led by a consultant dermatologist. However, it is important that all involved are aware of the various measures to help avoid unnecessary exposure to these potent teratogens during pregnancy. Every oral retinoid has a dedicated and specific Pregnancy Prevention Programme (PPP).

Key PPP features:

- All women should be made aware of the teratogenic risks before starting treatment
- Pregnancy must be excluded before treatment with oral retinoids
- Pregnancy test results (with a minimum sensitivity of 25 mIU/mL) must be documented 3 days or less before the prescription is issued
- Women of childbearing potential should be on at least one, or preferably two, complementary forms of effective contraception (eg, barrier and hormonal)
- Contraception should start 1 month before treatment, and should continue throughout oral retinoid treatment and after until the retinoids have left the patient's system—ie:

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    - At least 1 month after stopping treatment with isotretinoin or alitretinoin
    - At least 2 years after stopping treatment with acitretin
- Females should undergo a pregnancy assessment every 4 weeks at follow-up appointments
- Specialist advice from a physician specialised in teratology must be sought immediately if a pregnancy occurs
- Prescription of oral retinoids should be limited to 30 days' treatment
- The prescription must be dispensed within 7 days of issue
- Available data suggest that maternal exposure from the semen of patients receiving an oral retinoid is not associated with teratogenic effects

Acitretin

The measures are the same for all three products, with one exception: acitretin has a substantially longer half-life and duration of effect than either isotretinoin or alitretinoin, and therefore the PPP measures must also be undertaken for considerably longer.

The choice of contraception is particularly important for acitretin because it must be used throughout the treatment period and for at least 2 years after the patient has completed her course. These patients must also have regular follow-up appointments with their dermatology prescriber every 3 months during the 2-year period after treatment with acitretin has stopped to ensure patients are continuing to use contraception effectively.

We would like to remind healthcare professionals that measures for the prevention of pregnancy are imperative, with particular attention required for the longer supervision of patients who receive acitretin.

BNF section 13 Skin (http://www.bnf.org/bnf/search.htm?q=oral+retinoids)

Article citation: Drug Safety Update June 2013 vol 6, issue 11: H1.

Stop press

S1 Codeine: restricted use as analgesic in children and adolescents after European safety review

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.

Advice for healthcare professionals:

- 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

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- 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

Further information:

This information will be circulated via the NHS Central Alerting System (https://www.cas.dh.gov.uk) in early July.

Information from the European Medicines Agency: http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2013/06/news_detail_001813.jsp&mid=WC0b01ac058004d5c1

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