IRISH MEDICINES BOARD

Drug Safety NEWSLETTER

55TH EDITION

Diclofenac: the same cardiovascular precautions now apply for diclofenac as for selective COX-2 inhibitors

NSAIDs are valuable therapeutic agents in the treatment of pain and inflammation and the benefit-risk profile of these medicines has been closely monitored nationally and at EU level. EU reviews carried out in 2005, 2006 and 2012 confirmed that NSAIDs as a class are associated with a small increased risk of arterial thromboembolic events (such as myocardial infarction or stroke), particularly if used at high dose and for long-term treatment. The product information for all NSAIDs warns of this risk and class labelling recommends that NSAIDs be used at the lowest effective dose for the shortest period of time necessary to control symptoms.

Data from the previous reviews suggested an increased relative risk of arterial thrombotic events which was sometimes greater than for other commonly prescribed NSAIDs and in some cases as great or greater than that seen with certain COX-2 inhibitors ('coxibs'). Limitations in the data available at that time made it difficult to quantify the risk initially, but a consistent picture was emerging by the time of the 2012 review. The latest EU review by the Pharmacovigilance Risk Assessment Committee (PRAC) was therefore initiated specifically to assess the benefit-risk balance of systemic diclofenac and to consider whether further risk minimisation measures were warranted to mitigate the risk of cardiovascular adverse effects.

The PRAC has now reviewed the available data including several new case-control and cohort studies, a post-hoc analysis of data from the MEDAL (Multinational Etoricoxib and Diclofenac Arthritis Long-term) programme,[1] and a meta-analysis by the Coxib and traditional NSAID Trialists Collaboration[2] which involved over 600 clinical trials. The latter found that compared with placebo, the risk of major vascular events were increased by about one third by a coxib (rate ratio [RR] 1.37, 95% confidence interval [CI] 1.14-1.66; p=0.0009) or diclofenac (1.41, 1.12-1.78; p=0.0036), mainly due to an increase in major coronary events (coxibs: 1.76, 1.31-2.37; p=0.0001; diclofenac: 1.70, 1.19-2.41; p=0.0032). Overall, compared with placebo, allocation to diclofenac or a coxib caused around three additional major vascular events per 1000 participants per year, with one such event causing death; in high-risk individuals, about seven or eight more would have a major vascular event, of which two would be fatal. Although the risk is likely to be dose-dependent, the PRAC considered that cardiovascular thrombotic risk cannot be excluded across all doses of diclofenac, especially in patients with pre-existing co-morbidities.

Diclofenac is effective in reducing inflammation and pain. However, as the cardiovascular risk with systemic diclofenac appears similar to that of selective COX-2 inhibitors, it was considered that relevant risk minimisation measures in place for COX-2 inhibitors with respect to cardiovascular risk should also apply to diclofenac. The product information for all systemic diclofenac products will be updated to reflect this information and a Direct Healthcare Professional Communication (DHPC) will be distributed by Marketing Authorisation Holders.

Advice to Healthcare professionals

- Currently available data indicate that the risk of arterial thromboembolic events with diclofenac is comparable to selective COX-2 inhibitors ('coxibs').

In this edition

- Use of diclofenac is now contraindicated in patients with ischaemic heart disease, peripheral arterial disease, cerebrovascular disease or congestive heart failure. Patients with these conditions should have their treatment reviewed.
- Treatment with diclofenac should only be commenced after consideration of each individual's risk factors for cardiovascular events (e.g. hypertension, diabetes, hyperlipidaemia and smoking).
- The lowest effective dose should be used for the shortest duration possible to control symptoms.

Key Message

- **Clinical trial and epidemiological data consistently point towards an increased risk of arterial thrombotic risks associated with the use of diclofenac, similar to that for selective COX-2 inhibitors**
- **Diclofenac is now contraindicated in patients with established congestive heart failure (New York Heart Association, NYHA, classification II–IV), ischaemic heart disease, peripheral arterial disease or cerebrovascular disease. Patients with these conditions should have their treatment reviewed.**
- **Patients with significant risk factors for cardiovascular events (e.g. hypertension, hyperlipidaemia, diabetes mellitus, and smoking) should only be treated with diclofenac after careful consideration of the benefit-risk balance.**
- **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.**

1 Cannon PC et al. Cardiovascular outcomes with Etoricoxib and Diclofenac in patients with osteoarthritis and rheumatoid arthritis in the MEDAL programme: a randomized comparison. Lancet 2006, 368: 1771-1781

2 http://www.ctsu.ox.ac.uk/research/meta-trials/cnt/cnt-protocol

* *Brands available in Ireland include Difene, Diclac, Voltarol. Further information is available from* ***www.imb.ie****.*

Codeine: Restricted use as an analgesic in children and adolescents

The use of codeine for analgesia in children and adolescents under 18 has been restricted after an EU review.[1] This review was triggered by reports in 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 into morphine (which is responsible for its pharmacological effects) by the cytochrome P450 enzyme *CYP2D6*. 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.

Symptoms of morphine toxicity include somnolence, reduced levels of consciousness, lack of appetite, nausea and vomiting, constipation, respiratory depression and 'pin-point' pupils.

Advice to healthcare professionals

- Although morphine-induced side effects may occur at all ages, the current evidence suggests that children under 12 years of age are at special risk of life-threatening respiratory depression with codeine. There also seems to be a particular risk in those paediatric patients who might already have compromised airways and who require pain relief following tonsillectomy and/or adenoidectomy.
- Codeine-containing medicines should only be used to treat acute, moderate pain in children **older than 12 years of age, and only** if it cannot be relieved by other analgesics such as paracetamol or ibuprofen, because of the risk of respiratory depression associated with codeine use.
- Codeine is now contraindicated in all patients younger than 18 years of age for pain relief following tonsillectomy and/or adenoidectomy for Obstructive Sleep Apnoea Syndrome (OSAS) due to an increased risk of developing serious and life-threatening adverse reactions including loss of consciousness and respiratory depression.
- Codeine is contraindicated in patients of any age who are known to be *CYP2D6* ultra-rapid metabolisers.
- Use of codeine is contraindicated in breastfeeding women due to an increased risk for the child if the mother is an ultra-rapid metaboliser.
- Codeine is not recommended in children with neuromuscular disorders, severe cardiac or

respiratory conditions, upper respiratory or lung infections, multiple trauma or extensive surgical procedures. Symptoms of morphine toxicity may be increased in these patients.
- Codeine use for all patients should be at the lowest effective dose for the shortest period of time and the duration of treatment should be limited to 3 days. Healthcare professionals are reminded that patients may respond differently to codeine. Those caring for patients taking codeine should be advised to seek medical advice if symptoms of toxicity occur.
- The product information for codeine-containing medicines will be updated to reflect this information.

Key Message
- **Use of codeine is contraindicated in patients younger than 18 years of age for pain relief following tonsillectomy and/or adenoidectomy for OSAS and in those known to be *CYP2D6* ultra-rapid metabolisers.**
- **Codeine containing medicines should only be used in children over 12 years old to treat acute moderate pain, and only if the pain cannot be relieved by other pain killers such as paracetamol or ibuprofen alone.**

1 Restrictions on the use of codeine for pain relief in children European Medicines Agency press release 28th June 2013. (http://www.ema.europa.eu/docs/en_GB/document_library/Press_release/2013/06/WC500144851.pdf)

* *Brands include Nurofen plus, Migraleve, Feminax, Kapake, Solpadeine.. See www.imb.ie for further details.*

Dianette (cyproterone acetate 2mg /ethinylestradiol 35 micrograms) – new risk minimisation measures to further mitigate the known risk of thromboembolism

An EU review of Dianette (cyproterone acetate 2 mg, ethinylestradiol 35 micrograms), a treatment for acne and other hormone related conditions, has concluded that the benefits continue to outweigh the risks, provided that a number of measures are taken to minimise the well known risk of thromboembolism.

This medicine should now be used solely in the treatment of moderate to severe acne related to androgen sensitivity or hirsutism in women of reproductive age. Furthermore, Dianette should only be used for the treatment of acne when alternative treatments, such as topical therapy and oral antibiotic treatment, have failed.

The progestogen content of Dianette (i.e. cyproterone acetate), suppresses ovulation and therefore also has a contraceptive effect, although it is not authorised as a contraceptive in its own right. Concomitant use of Dianette with another hormonal contraceptive will expose women to a higher dose of oestrogen and increase the risk of thromboembolism and so must not be taken in combination.

The risk of thromboembolism occurring with these medicines is low and well known. The review concluded that the risk of venous thromboembolism (VTE) and arterial thromboembolism (ATE) is increased in users of Dianette, with the excess risk of VTE being highest during the first year a woman starts treatment, or when restarting or switching after a pill-free interval of at least a month. There is evidence from epidemiological studies that the incidence of VTE is 1.5 to 2 times higher in users of Dianette than in users of levonorgestrel-containing combined hormonal contraceptives (CHCs) and may be similar to the risk for desogestrel, gestodene and drosperinone containing CHCs.

Advice to Healthcare Professionals

- Dianette should now be used solely in the treatment of moderate to severe acne related to androgen sensitivity or hirsutism in women of reproductive age. For the treatment of acne, Dianette should only be used when alternative treatments, such as topical therapy or oral antibiotic treatment have failed.
- Since Dianette is a hormonal contraceptive, women should not take this medicine in combination with other hormonal contraceptives.
- It is important that healthcare professionals and women using Dianette are aware of the risk of VTE in order to prevent complications and serious adverse outcomes and to facilitate a timely and correct diagnosis of VTE. Educational materials will also highlight risk factors for VTE include increasing age, smoking and immobility.

Key Message
New risk minimisation measures are being introduced to further mitigate the known risk of thromboembolism for Dianette, a treatment for acne and hirsutism containing cyproterone acetate 2 mg, ethinylestradiol 35 micrograms.

Lariam (mefloquine): Updated product information and availability of guidelines for healthcare professionals/ alert cards for patients

Lariam (mefloquine) is an anti-malarial product currently authorised in Ireland for:

- The treatment of *P.Falciparum* malaria in which the pathogen has become resistant to other anti-malarial agents.
- For chemoprophylaxis i.e. prophylaxis of malaria in people travelling to malarious areas in which multiple resistant *P.Falciparum* strains occur.

The potential for Lariam to induce potentially serious neuropsychiatric disorders was first identified a number of years ago and has been the subject of previous reviews/updates at European and National level. As part of the on-going monitoring of its benefits and risks, a further review of cumulative safety data was concluded at EU level in April 2013. This review reaffirmed the known risks associated with use of mefloquine but recommended further updates to the product information and provision of supplementary educational materials.

These supplementary materials should be read in conjunction with the current version of the product information (Summary of Product Characteristics which is available at www.imb.ie). Healthcare Professionals are additionally reminded of the following recommendations:

- Lariam should not be used for malaria chemoprophylaxis in patients with active or a history of psychiatric disturbances.
- Lariam (mefloquine) may induce potentially serious neuropsychiatric disorders.
- The most common neuropsychiatric reactions to Lariam include abnormal dreams, insomnia, anxiety, and depression. Additionally hallucinations, psychosis, suicide, suicidal thoughts and self-endangering behaviour have been reported.
- Patients should be advised that if they experience a neuropsychiatric reaction such as suicidal thoughts; self-endangering behaviour; severe anxiety; feelings of restlessness, confusion, or mistrust towards others; visual/auditory hallucinations; depression; or changes to their mental state during treatment, they should stop taking Lariam immediately and seek urgent medical advice.
- Healthcare professionals should react promptly to signs of neuropsychiatric reactions with Lariam It should be discontinued immediately and replaced by alternative malaria prophylaxis medication.
- Due to the long half life of Lariam, adverse reactions may occur and persist up to several months after discontinuation of the drug.
- The Guide for Healthcare Professionals should be read and the checklist followed before prescribing Lariam for any patient.

Advice for Healthcare Professionals

- Be aware of the prescribing recommendations and contraindications for the appropriate use of Lariam as outlined in the Summary of Product Characteristics (SPC).
- A guide for healthcare professionals entitled "Lariam (Mefloquine) for Malaria Chemoprophylaxis", a checklist for the prescription of Lariam and a Lariam patient alert card have all been made available by the Marketing Authorisation Holder.
- These prescribing tools are intended to act as a resource to aid prescribing decisions and monitoring in patients and should be used in conjunction with the prescribing information A "Lariam patient alert card" should be given to all patients.
- Please report suspected adverse reactions associated with Lariam to the IMB, via the online reporting/downloadable form options (www.imb.ie) or by telephone (01-6764971).

Key Message
The prescribing and monitoring advice for appropriate use of Lariam should be followed.

Hydroxyethylstarch (HES) Infusion Solutions: PRAC recommends suspension of licenses

Hydroxyethyl starch (HES) containing products are synthetic colloid solutions used for plasma volume expansion in a range of clinical settings. In Ireland, marketed HES products are EquiHes, HyperHAES, Voluven and Volulyte.

The EU Pharmacovigilance Risk Assessment Committee (PRAC) has reviewed the balance of benefits and risks of HES products in different patient groups. The review concluded that there is clear indication of harm when HES is used for fluid resuscitation, and no evidence of a greater benefit, compared with crystalloid solutions. The PRAC concluded that the risks HES products pose to patients outweigh the benefits in all clinical settings.

The assessment considered the results of three recently published studies [1], [2], [3] that compared the use of HES with the use of crystalloids in critically ill patients and in particular, patients with severe sepsis. The studies in patients with severe sepsis treated with HES showed a consistent pattern of harm in terms of

increased mortality and adverse renal effects [1], [2]. A large study targeting a broader critically ill population indicates similar effects with no benefit, but with harm in terms of renal adverse effects [3]. 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 crystalloids [4]. A Cochrane review [5] 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 crystalloids.

Although a formal EU regulatory position will not be available until the autumn of this year, the IMB would **not** recommend the use of these products in any clinical setting, pending further regulatory advice recommendations.

Advice for healthcare professionals

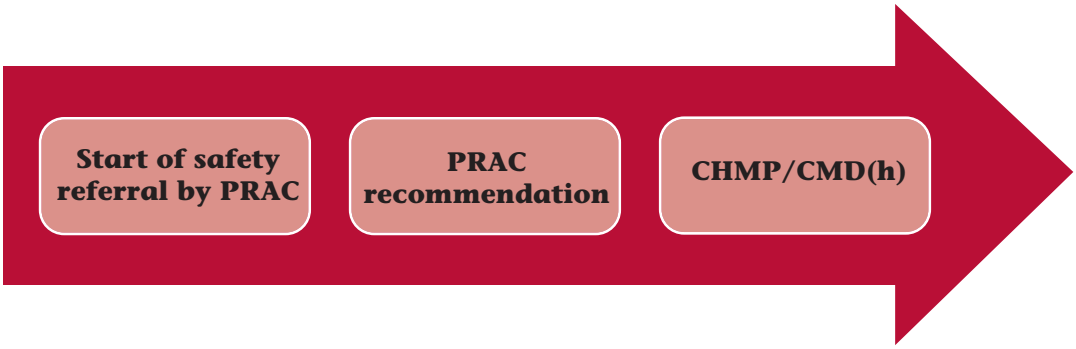
- Results from large, randomised clinical trials have reported an increased risk of renal dysfunction and mortality in critically ill or septic patients who received HES compared with crystalloids.
- Following an EU review of the benefits and risks of HES infusion solutions, the PRAC has recommended that the marketing authorisations for these products should be suspended. This is not the final step in the procedure and a final regulatory decision is anticipated in the autumn.

Key Message
Following the PRAC recommendation for suspension of marketing authorisations for HES infusion solutions, the IMB would not recommend that these products be administered to patients, pending the finalisation of the regulatory procedure.

1 *Brunkhorst, F. M., C. Engel, et al. Intensive insulin therapy and pentastarch resuscitation in severe sepsis. N Engl J Med 2008; 358(2): 125-39.*
2 *Perner, A., N. Haase, et al. Hydroxyethyl starch 130/0.42 versus Ringer's acetate in severe sepsis. N Engl J Med 2012; 367(2): 124-34.*
3 *Myburgh, J. A., S. Finfer, et al. Hydroxyethyl starch or saline for fluid resuscitation in intensive care. N Engl J Med 2012;367(20): 1901-11*
4 *Zarychanski R, et al. JAMA 2013; 309: 678-88*
5 *Perel P, et al. Cochrane Database Syst Rev 2013; 2: CD000567.*

PRAC Recommendations

Recent editions[1,2] of the IMB Drug Safety Newsletter (DSN) have highlighted the role of the Pharmacovigilance Risk Assessment Committee (PRAC), a new scientific committee established within the framework of revised pharmacovigilance legislation which came into effect in July 2012. As previously outlined, the PRAC meets on a monthly basis over a four-day period (Monday – Thursday) to discuss issues related to the risk management of medicines for human use and is responsible for providing recommendations to other relevant EMA Committees on any question relating to pharmacovigilance activities in respect of medicinal products for human use.



As part of the transparency provisions within the legislative framework, brief high level outcomes from PRAC meetings are made publically available once meetings are over. These outcomes are published on the Friday following the meeting and are highlighted by the IMB on its website, with a link to relevant publications, once available. Final recommendations, together with agendas and adopted minutes of the PRAC meetings are also made publicly available via the EMA and IMB websites.

1 *Drug Safety Newsletter 50th Edition. October 2012*
2 *Drug Safety Newsletter 53rd Edition. May 2012*

Direct Healthcare Professional Communications published on the IMB website since the last Drug Safety Newsletter

Product	Safety Issue
Hydroxyethyl Starch containing solutions	IMB Opinion on the PRAC recommendation to suspend the marketing authorisations of HES containing solutions.
Revlimid (Lenalidomide)	Communication on important aspects in the clinical use of Revlimid.
Durogestic DTrans Transdermal patch (Fentanyl)	Introduction of new warning-Serotonin syndrome may occur under co-administration with serotonergic drugs.
Trobolt (retigabine)	Treatment may lead to pigment changes of ocular tissues, including retina, and skin, lips and/or nails.
Dianette (Cyproterone acetate/ ethinylestradiol)	Communication on strengthening of warnings, new contraindications and updated indication.
Sublimaze (Fentanyl)	Introduction of new warning serotonin syndrome may occur under co-administration with serotonergic drugs.
Questran (Cholestyramine resin)	Communciation on recall of Questran 4g/sachet Powder for Oral Suspension due to possible contamination with *enterococcus faecium.*
Avastin (Bevacizumab)	Communication on cases of necrotising fasciitis reported with Avastin
Synacthen (tetracosactide)	Communication to health care professionals about the availability of Synacthen 0.25 mg/ml (tetracosactide) and Synacthen Depot 1 mg/ml (tetracosactide).
Protelos (Strontium Ranelate)	Important new restriction for the use of Protelos (strontium ranelate) following new data showing an increased risk of myocardial infarction.

Registration/Notification Reminder

Have you submitted your email details or registered with the IMB website to allow you to continue to receive the Drug Safety Newsletter (DSN) electronically? As highlighted in the IMB's 53rd Edition published in May, the IMB intends to phase out postal distribution of the DSN over the coming months and to make electronic distribution the main method of circulation, to ensure important safety updates are issued promptly. To ensure you can continue to receive all issues of the DSN, please register on the IMB website (**www.imb.ie**) to receive an alert when a new issue is published, or submit your email address to **imbpharmacovigilance@imb.ie**, to allow an electronic version to be emailed directly to you. Registration on the IMB website also allows you to receive other information/alerts issued by the IMB.

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