IRISH MEDICINES BOARD

Drug Safety NEWSLETTER

51ST EDITION

Diclofenac – Further evidence that the cardiovascular risk with diclofenac is higher than other non-selective NSAIDs and similar to the selective COX-2 inhibitors

Diclofenac is a widely used non-selective non-steroidal anti-inflammatory drug (NSAID), authorised for the relief of pain and inflammation in a wide range of conditions, including arthritic conditions and acute musculoskeletal disorders. It is available in Ireland and throughout the European Union in a number of different formulations (oral, parenteral, suppositories, topical etc.) Most preparations are for systemic use and are available as prescription medicines, with topical preparations also available as over the counter medicines in pharmacies. In October 2012, a review of the available scientific data on the cardiovascular risk of non-selective non-steroidal anti-inflammatory drugs (NSAIDs) was completed at EU level.[1]

This review largely confirmed the findings of a previous 2006 review in relation to the cardiovascular risks of non-selective NSAIDs. For diclofenac in particular, the new evidence continues to point towards an increased risk of thrombotic events that is similar to that of coxibs. Whilst, there is some evidence of an increased risk with naproxen and ibuprofen, this is still considered to be lower than the risk with diclofenac or selective Cox-2 inhibitors.The need to update the existing treatment advice for diclofenac is now being assessed and pending an update on the outcome of this assessment.[2] Diclofenac should be prescribed in accordance with the known risks and at the lowest effective dose for the shortest possible time.

Advice for Healthcare Professionals

- When prescribing NSAIDs, patients should use the lowest effective dose for the shortest duration of time necessary to control their symptoms. The need for long-term treatment should be reviewed periodically.
- Prescribers should note the information on cardiovascular safety and other risks in the product information for non-selective NSAIDs. They should follow the relevant precautions and take account of the known level of risk with each medicine when selecting a suitable treatment for individual patients.
- People with risk factors for cardiovascular events may be at higher risk of thrombotic adverse events, but some increased cardiovascular risk may apply to all NSAID users, including those at low estimated cardiovascular disease risk.
- Adverse effects may manifest early, and the risk may persist throughout treatment.
- The greatest concern relates to chronic use of high doses (especially for coxibs and diclofenac).

Key Message

- **A review of data indicates a consistent but small increase in the risk of cardiovascular adverse effects with diclofenac compared with other non-selective NSAIDs, similar to the risk with COX-2 inhibitors.**
- **As a follow-on to this review, the EMA's new Pharmacovigilance Risk Assessment Committee (PRAC) will now assess all available data on diclofenac (both published and unpublished) to consider the need for updated treatment advice.**
- **The outcome of the current review will be communicated when available and existing treatment advice will be updated if necessary.**

References

1. http://www.ema.europa.eu/docs/en_GB/document_library/press_release/2012/10/WC500134090.pdf.
2. http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2012/10/news_detail_001637.jsp&mid=WC0b01ac058004d5c1.

In this edition

Valdoxan (agomelatine) – Reports of serious hepatotoxicity

Agomelatine is a melatonergic agonist, indicated in the treatment of major depressive episodes in adults, which was authorised for use across the EU through a common assessment procedure in February 2009. Agomelatine exerts its pharmacological effect by agonist activity at the melatonin MT1 and MT2 receptors, and antagonism at the serotonin 5-HT2C receptor, thereby increasing levels of dopamine and noradrenaline in areas of the brain involved in mood control.

Due to the potential for hepatotoxicity, the product information has since first authorisation included a requirement for regular monitoring of liver function tests in patients treated with agomelatine. Since then, cases of liver injury, including hepatic failure, elevations of liver enzymes exceeding 10 times the upper limit of normal, hepatitis and jaundice have been reported in patients treated with agomelatine. The majority of these abnormalities occurred during the first months of treatment. The pattern of liver damage appears mainly hepatocellular. When agomelatine was discontinued, the serum transaminases usually returned to normal levels. Agometaline should be immediately discontinued if an increase in serum transaminases exceeds 3 times the upper limit of normal, or if patients present with symptoms or signs of potential liver injury.

The data available for agomelatine from clinical trials and post-marketing experience was recently reviewed at EU level. The review indicated that in clinical studies, elevations of transaminases (>3 times the upper limit of the normal range) have been observed in patients treated with agomelatine, particularly those receiving a 50 mg dose (2.5% versus 1.4% with 25 mg) and additionally considered the serious cases of hepatotoxicity (including six reports of hepatic failure) reported with agomelatine post marketing. Some of the patients treated in the context of post-marketing experience presented with hepatic reactions following an increase in the dosage.

The review concluded that the product information for agomelatine should be strengthened by including new warnings, additional monitoring of liver function tests when increasing the dosage and a reminder of existing warnings relative to liver function. Prescribers are also reminded that agomelatine is contraindicated in patients with hepatic impairment, ie, cirrhosis or active liver disease.

Advice for Healthcare Professionals

- Cases of serious hepatotoxicity, including six cases of hepatic failure have been reported in association with post-marketing use of agomelatine.
- Liver function tests (LFTs) should be monitored in all patients receiving agomelatine, as follows:
  - at initiation of treatment.
  - periodically at 3 weeks, 6 weeks (end of acute phase), 12 weeks, 24 weeks (end of maintenance phase) and thereafter
  - when increasing the dose of agomelatine at the same time intervals that apply to initiation of treatment
  - whenever clinically indicated
- Any patient who develops increased serum transaminases should have their LFTs repeated within 48 hours.
- Agomelatine should be immediately discontinued if an increase in serum transaminases exceeds 3 times the upper limit of normal, or if patients present with symptoms or signs of potential liver injury.
- Caution should be exercised when prescribing agomelatine to patients with pre-treatment elevated transaminases levels (> the upper limit of the normal ranges and ≤3 times the upper limit of the normal range). Agomelatine should **not** be initiated in patient with pretreatment elevated transaminases > 3 times the upper limit of the normal ranges.
- Caution should be exercised when prescribing agomelatine for patients with hepatic injury risk factors, eg obesity/overweight/non-alcoholic fatty liver disease; diabetes, substantial alcohol intake or use of concomitant medicines associated with risk of hepatic injury.
- Patients should be informed of the symptoms of potential liver injury and advised to stop taking agomelatine immediately and to seek urgent medical advice if these symptoms appear.
- Prescribers are also reminded that agomelatine is contraindicated in patients with hepatic impairment, i.e., cirrhosis or active liver disease.
- Any suspected adverse reactions associated with the use of agomelatine should be reported to the IMB in the usual way.

Key Message

- **Cases of hepatoxicity, including six cases of hepatic failure have been reported in association with post-marketing use of agomelatine.**
- **LFTs should be monitored in all patients during treatment, in line with the revised recommendations above.**
- **Treatment should be immediately discontinued if an increase in serum transaminases exceeds the ULN x3 or in patients presenting with symptoms of liver injury.**
- **Patients should be informed of the symptoms of liver injury and of the need for immediate action if these symptoms appear.**

Evicel – Recommendations to minimise the risk of gas embolism during application

Evicel is a medicinal product which is used as a fibrin sealant (glue) and was authorised for use in Ireland and a number of other EU Member States in 2008. It is used by surgeons to reduce local bleeding during surgery when standard techniques are not sufficient. Evicel is supplied in a package containing two solutions, one containing the active substance fibrinogen (50 to 90 mg/ml), and the other containing the active substance thrombin (800 to 1200 International Units per millilitre), which are then combined together. The solution is then sprayed using either pressurised air or carbon dioxide.

An EU review of the available safety data, in particular reported cases of confirmed or suspected gas embolism associated with the use of spray devices that use a pressure regulator to administer these medicines was undertaken in May 2012.. This review concluded that while rare, reports of gas embolism appear to be related to the use of the spray devices at higher than recommended pressures and/or closer than recommended proximity to the tissue surface. Accordingly, a number of additional risk minimisation measures for fibrin sealants like Evicel were recommended, when these medicines are applied as spray during surgery, as outlined below:

Advice for Healthcare Professionals

- Evicel should be sprayed using CO_2 only, instead of pressurised air, because the greater solubility of CO_2 in blood reduces the risk of embolism
- Evicel should not be sprayed in endoscopic surgery. When used in laproscopic surgery, care should be taken to ensure that the minimum safe distance from tissue is observed
- The product information for Evicel will be updated with clear and consistent advice for healthcare professionals regarding recommended pressure and distance to use during spraying application

Key Message

- **The risk of gas embolism associated with use of Evicel is rare and appears to be related to the use of the spray devices at higher than recommended pressures and/or closer than recommended proximity to the tissue surface**
- **Evicel should be sprayed using CO2 only, because the greater solubility of CO2 in blood reduces the risk of embolism**
- **The product information for Evicel is currently being updated to include information on the recommended pressure and distance to support safe use**

Exempt Medicinal Products – Prescribing products that have been suspended in Ireland for safety reasons

Subject to certain exemptions, medicinal products which are placed on the Irish market are required to have a Marketing Authorisation issued by the IMB (reflected by a PA number) or, for certain medicines authorised for all member states of the EU, an authorisation issued by the European Commission, reflected by an EU number (see also regulation 6 of the Medicinal Products (Control of Placing on the Market) Regulations 2007). Schedule 1 to these regulations includes an exemption for practitioners to prescribe unauthorised medicinal products for individual patients under their direct responsibility, in order to fulfil the special needs of those patients. Such products are referred to as "exempt medicinal products".

The sourcing and prescribing of exempt medicinal products is referred to in the following Regulations:

- Medicinal Products (Control of Placing on the Market) Regulations 2007 S.I. 540/2007 as amended
- Medicinal Products (Control of Wholesale Distribution) Regulations 2007 S.I. 538/2007 as amended
- Medicinal Products (Control of Manufacture) Regulations 2007 S.I. 539/2007 as amended

An 'exempt medicinal product' is defined as "a medicinal product to which paragraph 2 of Schedule 1 to the Medicinal Products (Control of Placing on the Market) Regulations 2007, or any equivalent legislation in any EEA State other than the State, applies". The aforementioned Paragraph 2 of Schedule 1 states that an exempt medicinal product may be sold or supplied "..in response to a bona fide unsolicited order, formulated in accordance with the specifications of a practitioner for use by his individual patients on his direct personal responsibility, in order to fulfil the special needs of those patients…".

It has come to the attention of the IMB that products containing certain active ingredients that have had their marketing authorisations suspended and/or revoked in Ireland, and other markets, due to safety concerns, continue to be prescribed in a small number of cases for Irish patients. This practice, as outlined above, is carried out under the responsibility of the prescriber, and as such, it is recommended that prescribers research any safety concerns surrounding exempt medicinal products they prescribe and any risk management plans that may be in operation in the markets where the products remain available.

User Reporting of Medical Device Incidents

The medical device vigilance system was set up under the medical device directives to minimise risks to the safety of patients, users and others.

The vigilance system achieves its objectives in several ways:

- through manufacturers and users submitting vigilance reports to the relevant competent authorities (the IMB in Ireland);
- through the evaluation of reported incidents by the competent authorities;
- through the dissemination of information, which may be used to prevent recurrence of the incident, or to alleviate the consequences of such incidents, in cases when it is necessary to do so;
- by the device being updated, modified or taken off the market in cases when it is necessary to do so.

There is a mandatory requirement for manufacturers to report vigilance issues in line with the European Guidelines on a medical devices vigilance system (MEDDEV 2.12-1).

In relation to user reporting, the IMB currently operates a voluntary system whereby a user, healthcare professional or any other person who identifies a medical device safety issue can report it to the IMB. We strongly encourage healthcare professionals and members of the public who have encountered a safety issue with a medical device that they have used to report the issue to us.

Increased levels of reporting from healthcare professionals and other device users may help in the early detection of adverse trends or safety issues. When the IMB receives reports of safety issues from users or the public, we are obliged by the medical devices directives to ensure that the manufacturer of the device concerned, or his authorised representative, is also informed of the report. The source of the report will not be disclosed without prior permission.

Reports relating to safety issues or concerns about medical devices can be made by healthcare professionals or by members of the public by completing a 'Medical Device Incident User Report form' or by submitting a report through the IMB's online reporting system, both of which are available on the IMB website **www.imb.ie**. Users may also report medical devices safety issues to the IMB by post (Irish Medicines Board, Kevin O'Malley House, Earlsfort Centre, Earlsfort Terrace, Dublin 2), by email (vigilance@imb.ie) or by telephone (01 6764971).

See enclosed insert for our Quick Guide to Medical Device Incident User Reporting

View the Drug Safety Newsletter online or via email

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

Product	Safety Issue
Caelyx (pegylated liposomal doxorubicin)	Reintroduction of supply through the Caelyx Managed Access Programme (CMA)
Tamiflu (oseltamivir) Oral Suspension	Concentration change from 12mg/ml to 6mg/ml. The dispenser will be changes from milligrams (mgs) to milliliters (mLs)
Valdoxan (agomelatine)	Recommendations for the importance of liver function monitoring
Trimetazidine containing products	Information regarding the restriction of indications for Trimetazidine containing products
Xgeva (denosumab)	Risk of symptomatic hypocalcaemia