IRISH MEDICINES BOARD

Drug Safety NEWSLETTER

40th EDITION

Multaq (dronedarone) – Association with Severe Liver Injury

Dronedarone is indicated in clinically stable adult patients with a history of, or current non-permanent atrial fibrillation (AF) to prevent recurrence of AF or to lower ventricular rate.

Since dronedarone was licensed in 2009, there have been reports of liver function test abnormalities and hepatocellular liver injury in patients taking dronedarone, including two cases of acute liver failure requiring transplantation. Some of these cases occurred early after the start of treatment, with the two cases requiring liver transplantation occurring at 4.5 and 6 months after initiation of treatment in patients with normal baseline liver function tests. In one case the liver injury was not reversible after discontinuation of dronedarone. Although both patients were taking concomitant medications, a causal relationship with dronedarone could not be excluded.

Following receipt of these reports, the Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA) has initiated a review of all available data concerning the possible risks of liver injury associated with the use of dronedarone and their impact on its benefit-risk balance.

The Committee discussed dronedarone during its January 2011 meeting and concluded that there was a need for urgent regulatory action to help manage the possible risk of severe liver complications with the medicine. The Committee recommended the inclusion of warnings and precautions in the medicine's prescribing information, to ensure appropriate monitoring of liver function before initiation of and during treatment with dronedarone, recommending that treatment is stopped if there are signs of potential liver damage.

Further evaluation of the data is continuing in the context of a formal EU wide referral procedure, the outcome of which will be communicated once the CHMP has reached its final opinion.

In the meantime, the new European regulatory recommendations are as follows:

Advice to Healthcare Professionals

- For patients prescribed dronedarone, liver function tests should be performed:
  - prior to initiation of treatment,
  - on a monthly basis for six months,
  - at months 9 and 12, and periodically thereafter.
- Patients currently receiving dronedarone should be contacted within the next month so that liver function tests could be performed and thereafter they should be tested as listed above depending on when treatment was initiated

In this edition

- If alanine transaminase (ALT) levels are elevated to ≥3 × upper limit of normal (ULN), levels should be re-measured within 48 to 72 hours. If ALT levels are confirmed to be ≥3 × ULN after re-measurement, dronedarone treatment should be withdrawn.

- Patients should be advised to contact healthcare professionals immediately in case of signs or symptoms of liver injury. Patients should be advised to immediately report any symptoms of potential liver injury (such as sustained new-onset abdominal pain, anorexia, nausea, vomiting, fever, malaise, fatigue, jaundice, dark urine or itching) to their physician.

The product information (Summary of Product Characteristics [SmPC] and package leaflet) will be revised to include this information. Updated educational materials will be distributed when available.

The current European public assessment report for Multaq can be found on the EMA website:
http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/001043/WC500044538.pdf

Key Message:
Cases of liver injury, including two cases of liver failure requiring transplantation have been reported in patients receiving dronedarone. Some of these cases occurred early after the start of treatment. For patients prescribed dronedarone, liver function tests should be performed:

- **prior to treatment,**
- **on a monthly basis for six months,**
- **at months 9 and 12, and periodically thereafter.**

Thelin (sitaxentan) – Marketing Authorisation withdrawal

Sitaxentan (Thelin) is an endothelin receptor antagonist, indicated for the treatment of patients with pulmonary arterial hypertension classified as WHO functional class III, to improve exercise capacity.

In December 2010 the marketing authorisation holder for Thelin announced its decision to withdraw the product from all markets worldwide and to discontinue all ongoing clinical trials. This decision was made after a review of fatal cases associated with hepatic injury, including a reported case from the UK (in 2009) and two cases from clinical trials in India and the Ukraine, which occurred in 2010.

Hepatic reactions are known side effects of sitaxentan, and warnings have been included in the product information and educational materials since it was first licensed. These warnings were updated to provide further guidance regarding hepatic safety monitoring after the fatal case which occurred in 2009. The new data suggest that serious hepatotoxicity in association with sitaxentan is idiosyncratic and cannot be prevented in all patients. In some patients, development of liver injury was not related to identifiable risk factors, was unlikely to be detected by monthly monitoring, and did not resolve when sitaxentan was discontinued. Based on the information available and the availability of alternative treatments, the marketing authorisation holder concluded that the overall benefit of Thelin no longer outweighed the risk in the general population of PAH patients and voluntarily withdrew the product from all markets worldwide.

Alternative treatments for pulmonary arterial hypertension are available in Ireland.

Advice was provided directly to prescribers indicating that patients should be switched to an alternative treatment as soon as is safely possible. The Dear Healthcare Professional Communication is available on the IMB website. **www.imb.ie.**

Fluoroquinolones and the risk of QT Prolongation

Fluoroquinolones are broad spectrum antibiotics, authorised for a wide range of indications. Those currently authorised in Ireland include: moxifloxacin, levofloxacin, ofloxacin and ciprofloxacin*.

The potential for fluoroquinolones to cause QT prolongation is recognised and has been previously considered on the basis of available data for the individual substances, as reflected in the product specific information. A further recent European review of study and post-marketing data in relation to QT prolongation and fluoroquinolones concluded that the risk of QT prolongation does not appear to be similar across this class of antibiotics, but that substances may be classified according to their potential to prolong QT interval and precipitate cardiac events (i.e. ventricular arrhythmia).

As moxifloxacin has been associated with an established potential for increased risk of QT prolongation, prescribers are reminded to use moxifloxacin only when it is considered inappropriate to use antibacterial agents that are commonly recommended or when these have failed for the treatment of: acute bacterial sinusitis, acute exacerbations of chronic bronchitis, community acquired pneumonia (except severe cases) and mild to moderate pelvic inflammatory disease.

Following assessment of the available evidence, levofloxacin, ofloxacin and ciprofloxacin are considered to have a lower potential to induce QT interval prolongation.

It is important to note that in the context of conditions which favour the development of QT prolongation e.g. hypokalaemia, hypomagnesaemia, bradycardia, patients with congenital or acquired QT prolongation, some fluoroquinolones have the potential to induce life-threatening Torsades de Pointes (e.g. moxifloxacin).

The product information for fluoroquinolones will be updated and harmonised throughout Europe in relation to the updated assessment of the risk of QT interval prolongation for the individual substances. For further information and the complete list of fluoroquinolones considered as part of the review please see the following link:

http://www.ema.europa.eu/docs/en_GB/document_library/Report/2011/01/WC500100459.pdf)

Key Message:

- **The risk of QT interval prolongation with fluoroquinolone antibiotics varies across the class**
- **Due to an increased risk of QT prolongation (in addition to the potential for other serious risks, i.e. serious hepatotoxicity), oral moxifloxacin should only be used when use of other antibacterial agents is inappropriate, or have failed.**
- **Consideration should be given to official guidance on the appropriate use of antibacterial agents.**

* Brands include:

Moxifloxacin – Avelox
Ofloxacin - Tarivid, Biravid
Levofloxacin – Tavanic, Tavager
Ciprofloxacin – Truoxin, Ciproxin

View the Drug Safety Newsletter online or via email

The IMB publishes an electronic version of the Drug Safety Newsletter on its website, **www.imb.ie**. Should you wish to receive an email alert notifying you that future editions of the newsletter are available online, please submit your request to **imbpharmacovigilance@imb.ie**. Alternatively the electronic version can be emailed directly to you. Signing up to this service will ensure you no longer receive a print version. The online edition is in PDF format, thus allowing you to save the newsletter and/or print specific pages. The online version will also contain hyperlinks to the product information and other documents on the IMB and EMA websites. By signing up to this environmentally friendly online service, you will receive prompt notification of publications and will assist the IMB to reduce postage, production and related costs.

Safe Use of Insulin Pens

The Medical Device Vigilance group of the IMB recently issued an Advisory Notice (available on **www.imb.ie**) outlining the potential risk of bloodborne pathogen transmission if insulin pens are used on more than a single patient, even if needles are changed between patients. Healthcare professionals are reminded that these products should be used in accordance with the recommendations in the device labelling/Summaries of Product Characteristics (SmPC) for the individual products.

Direct Healthcare Professional Communications

In the case of urgent and/or important safety issues about a medicinal product, a Direct Healthcare Professional Communication (DHPC) is used to notify healthcare professionals. A DHPC (also known as a 'Dear Doctor Letter') aims to ensure safe and effective use of a marketed medicine and is delivered directly to healthcare professionals by marketing authorisation holders or by competent authorities such as the IMB.

The initiative for issuing a DHPC can come from the European or National regulatory authorities or the marketing authorisation holder. Agreement is needed between the marketing authorisation holder and competent authorities on the content and format of the information with consideration of the supportive evidence, recipients, and distribution timetable.

DHPCs are an important communication tool that can aid education and risk management for healthcare professionals. Situations where a DHPC should be considered as part of the risk-management process include:

- Suspension, withdrawal, revocation of a marketing authorisation with recall of the medicine from the market for safety reasons
- Important changes to the Summary of Product Characteristics (SmPC) e.g. new warnings or contraindications, reduced recommended dose, or restricted indications or availability
- A change in the balance of benefits and risks for a medicine

DHPCs are published on the IMB website (**www.imb.ie**) under 'Publications' once they have been distributed. Recent DHPCs published on the IMB website are outlined below and will be listed in future issues of the Drug Safety Newsletter.

Further information can be found on the IMB website and/or in Volume 9A of The Rules Governing Medicinal Products in the European Union – *Guidelines on pharmacovigilance for medicinal products for human use* – which outlines the obligations of marketing authorisation holders and national competent authorities for pharmacovigilance of licensed medicines including guidance on risk communication and DHPCs.

Recent DHPCs published on the IMB website:

Product	Safety Issue
Dianeal, Extraneal and Nutrineal solutions for peritoneal dialysis	Potential presence of endotoxins and risk of aseptic peritonitis
Vistide (cidofovir)	Risk of serious adverse reactions with off-label use
Multaq (dronedarone)	Information on severe liver injury associated with use of Multaq
Cubicin (daptomycin)	Association with eosinophilic pneumonia
Gadolinium containing contrast agents	Information on the risk of Nephrogenic Systemic Fibrosis (NSF)

Correspondence/Comments should be sent to the

Pharmacovigilance Section, Irish Medicines Board,
Kevin O'Malley House, Earlsfort Centre, Earlsfort Terrace, Dublin 2.

Tel: 676 4971-7 Fax: 676 2517 Email: imbpharmacovigilance@imb.ie