IRISH MEDICINES BOARD

Drug Safety NEWSLETTER

44TH EDITION

Multaq (dronedarone) – Restriction of use and new monitoring requirements

The European Medicines Agency's Committee for Medicinal Products for Human Use (CHMP) has completed its benefit-risk assessment of Multaq (previously notified in IMB Drug Safety Newsletters 40 and 43, February and August 2011).

As a result of the emergence of safety issues in the postmarketing period (hepatic, lung, and the negative inotropic effect), new restrictions for the use of Multaq have been introduced to maintain a positive benefit-risk balance.

Multaq is now only indicated in adult clinically stable patients with paroxysmal or persistent atrial fibrillation (AF) for the maintenance of sinus rhythm after successful cardioversion. Multaq should only be prescribed after alternative treatment options have been considered.

Treatment should only be initiated and monitored by specialists to ensure that the benefit-risk balance is positive for patients at the time of initiation of Multaq and that patients remain eligible for treatment according to the new restrictions for use.

The following additional restrictions for use will also be included in the Summary of Product Characteristics (SPC):

Updates to Contraindications and Warnings

- Multaq is now contraindicated in patients with:
  - Unstable haemodynamic conditions
  - History of, or current heart failure or left ventricular systolic dysfunction
  - Permanent AF (AF duration ≥ 6 months or unknown, and attempts to restore sinus rhythm no longer considered by the physician)
  - Liver and lung toxicity related to the previous use of amiodarone
- Patients taking Multaq should be carefully monitored during treatment by regular assessment of cardiac, hepatic and pulmonary function (see the section below for further details).
- If patients develops any conditions which would lead to a contraindication, treatment with Multaq should be stopped.
- Patients currently taking Multaq should have their treatment reviewed at the next routine appointment to ensure that they remain eligible for Multaq treatment according to the revised prescribing information.
- Prescribers should adhere to the prescribing information regarding contraindications and warnings, in particular to be aware of the potential for interactions with and need for dose adjustments when Multaq is used with other medicinal products, including anti-coagulants and digoxin.

Updates to Monitoring Requirements

<u>Cardiovascular monitoring</u>

- Regular cardiac examinations including an ECG at least every six months should be performed in patients receiving Multaq. If AF reoccurs, discontinuation of Multaq should be considered.
- If patients develop permanent AF, treatment with Multaq should be discontinued.
- Patients should be carefully evaluated for symptoms of cardiac failure during treatment.
- Patients should be appropriately anti-coagulated as per clinical AF guidelines. International Normalised Ratio (INR) should be closely monitored after initiating Multaq in patients taking vitamin K antagonists as per the prescribing recommendations for these products.

In this edition

Hepatic monitoring

- Liver function tests should be performed prior to initiation of treatment with Multaq, after one week and after one month following initiation of treatment and then repeated monthly for six months, at months 9 and 12, and periodically thereafter.

Renal monitoring

- Plasma creatinine values should be measured prior to and seven days after initiation of Multaq.

Pulmonary monitoring

- Cases of interstitial lung disease including pneumonitis and pulmonary fibrosis have been reported in association with use of Multaq. Onset of dyspnoea or non-productive cough may be related to pulmonary toxicity. If pulmonary toxicity is suspected during treatment, relevant pulmonary examinations should be considered and treatment discontinued if pulmonary toxicity is confirmed.
- Patients should be instructed to seek medical advice in case of occurrence of new cardiac or pulmonary symptoms or signs of hepatic impairment.

This information has also been communicated via a Direct Healthcare Professional Communication, available at **www.imb.ie**

Suspected adverse reactions, particularly pulmonary or hepatotoxicity associated with the use of Multaq should be reported to the IMB via the usual routes.

Key Message

Multaq is now only indicated in adult clinically stable patients with paroxysmal or persistent atrial fibrillation (AF) for the maintenance of sinus rhythm after successful cardioversion.

Multaq should only be prescribed after alternative treatment options have been considered. Treatment with Multaq should be initiated and monitored only under specialist supervision

Prescribers should strictly adhere to the Multaq prescribing information regarding indication, contraindications and warnings.

Prescribers should follow the new monitoring requirements for safe use of Multaq.

MabThera (rituximab) – Association with fatal infusion related reactions in patients with rheumatoid arthritis

MabThera (Rituximab) is a monoclonal antibody licensed via a European assessment procedure in 1998 and is used in adults to treat non-Hodgkin's lymphoma, chronic lymphocytic leukaemia and rheumatoid arthritis (see Summary of Product Characteristics for full details of authorised indications).

Data from clinical trials in rheumatoid arthritis (RA) have shown that infusion related reactions are the most frequent reactions associated with use of MabThera and information has recently become available showing these infusion related reactions may be fatal in rare cases. The mechanism of these reactions is not fully elucidated. However, the majority of cases occur during the first infusion, which points towards a cytokine-release reaction, rather than IgE mediated hypersensitivity. Usually the reaction occurs within the first 2 hours. The cases with a fatal outcome have been reported with either first time use or with later infusions.

This safety information has been included in the Summary of Product Characteristics (SPC) for MabThera. The Direct Healthcare Professional Communication is available on **www.imb.ie**.

Advice to Healthcare Professionals

- Healthcare professionals should be aware that infusion related reactions have been fatal in rare cases in patients receiving MabThera for RA.
- Premedication with 100 methylprednisolone should be completed 30 minutes prior to MabThera initiation, and premedication consisting of analgesic/anti-pyretic (*e.g. paracetamol*) and an antihistamine (*e.g. diphenhydramine*) should always be administered before each infusion of MabThera.
- Patients with pre-existing cardiac conditions and patients who have experienced prior cardiopulmonary adverse reactions should be closely monitored.
- If anaphylaxis or any other serious hypersensitivity /infusion reaction occurs administration of MabThera should be stopped immediately, and appropriate medical management should be initiated.
- Any suspected adverse reactions associated with use of MabThera should be reported to the IMB via the usual routes, see **www.imb.ie** for further information.

Key Message

Fatal infusion related reactions in patients being treated with MabThera for RA have been reported in the post marketing setting. These have been reported both with first time use and with later infusions.

If anaphylaxis or any other serious hypersensitivity/infusion reaction occurs administration of rituximab should be stopped immediately, and appropriate medical management should be initiated.

Non-prescription cough and cold medicines for young children – New advice

The IMB recently informed healthcare professionals of new recommendations on the use of cough and cold medicines in children. The new advice follows a review of the safety and efficacy of these medicines in children and reflects an evolution in the therapeutic strategy over time for the management of coughs and colds in children rather than the emergence of any new safety concern.

It is recognised that colds and coughs occur frequently in children and are generally self-limiting. As there is no robust evidence regarding the efficacy of cough and cold medicines in children and given that there have been some reports of side effects globally with these medicines, the IMB recommends that non-prescription cough and cold medicines (containing the active ingredients listed below) are no longer used in children under the age of 6 years.

For children aged 6 years and over, the risk from these ingredients is reduced because they suffer from cough and cold less frequently and consequently require these medicines less often; with increased age and size, they may tolerate these medicines better; and they can usually say if the medicine is working. Therefore, non-prescription cold and cough medicines containing the above ingredients can continue to be available for these older children aged 6 to 12 years, but through pharmacies only.

Implementation of updated product information

The product information for these medicines is being updated to reflect the new advice. The introduction of cough and cold medicines with the updated labelling has already commenced for the 2011 cough and cold season, and these will continue to be introduced to pharmacies over the coming months. At this time, it is considered that a recall or an immediate withdrawal of products with the older labelling is not necessary, because of their established use over many decades.

These medicines can still be used in children aged between 6 and 12 years and in adults. Since the labelling for some of these products may also include dosing information for adults and older children on the same label, it is considered that during the forthcoming cough and cold season of 2011, any outstanding non-prescription cough and cold medicines with the old labelling may remain in place, until the new labelling has been fully phased in.

The letter sent to Healthcare Professionals is available on the IMB website along with a list of those products affected. The Summaries of Product Characteristics for these products have been updated to reflect the new recommendations and are also available on **www.imb.ie**.

Products which contain the active ingredients listed below but that are not authorised for the treatment of coughs and colds in children are not affected by the new recommendations. Also, single constituent paracetamol and ibuprofen-containing medicines are not affected by these changes.

Key Message
Cough and cold medicines containing the active ingredients below should not be used in children under six years.

For children aged 6-12 years, non-prescription medicines to treat cough and colds can continue to be considered where necessary. Care should be taken to ensure adherence to the maximum daily dose and to ensure that the product is not taken with other cough and cold medicines.

In the context of paediatric use, non-prescription cough and cold medicines containing the active ingredients listed below will continue to be available for use in children aged between 6 and 12 years, but in pharmacies only, where advice can be given regarding their use.

Active ingredients affected:

Antitussives: dextromethorphan and pholcodine*

Expectorants: guaifenesin and ipecacuanha

Nasal decongestants: oxymetazoline, phenylephrine, pseudoephedrine, xylometazoline and ephedrine

Antihistamines: brompheniramine, diphenhydramine, doxylamine and triprolidine

* Pholcodeine containing products are currently subject to an EU review on the benefits and risks of these products. The outcome will be communicated once available. The above recommendations apply to pholcodeine containing products in the interim pending any further changes.

Revlimid (lenalidomide) – Risk of second primary malignancies in authorised indication

Revlimid (lenalidomide) is an immunomodulating agent licensed via a European assessment procedure in 2007, for use in combination with dexamethasone for the treatment of multiple myeloma in patients who have received at least one prior therapy.

Based on an observation of a 4-fold higher incidence of second primary malignancies in newly diagnosed multiple myeloma patients treated with lenalidomide compared to controls, a review of the benefit-risk balance of Revlimid in the authorised indication was undertaken by the Committee for Human Medicinal Products (CHMP) of the EMA (See IMB Drug Safety Newsletter 42, June 2011).

In the authorised indication (in previously treated multiple myeloma patients), an increase was observed (3.98 per 100 patient-years in lenalidomide treated group versus 1.38 per 100 patient-years in the control group). Non-invasive SPM comprise basal cell or squamous cell skin cancers. Most invasive SPMs were solid tumour malignancies.

Based on these data, the risk of occurrence of second primary malignancies should be taken into account before initiating treatment with Revlimid. Physicians should carefully evaluate patients before and during treatment using standard cancer screening for occurrence of second primary malignancies and institute treatment as indicated.

Advice for Healthcare Professionals

- The risk of occurrence of second primary malignancies should be taken into account before initiating treatment with Revlimid.
- Physicians should carefully evaluate patients before and during treatment using standard cancer screening for the occurrence of second primary malignancies and institute treatment as indicated.
- Suspected adverse reactions, especially the occurrence of new cancers associated with the use of Revlimid should be reported to the IMB via the usual routes, see **www.imb.ie** for further details.

Key Message

A higher incidence of second primary malignancies has been observed in patients treated with Revlimid compared to controls, within the authorised indication.

The benefit-risk balance for Revlimid remains positive within its approved patient population however prescrib-ers should be aware of the risk of new cancers as a result of treatment with lenalidomide.

Vimpat (lacosamide) 15 mg/ml syrup – Discontinuation of supply

Vimpat has been authorised in the EU since 2008 for use as adjunctive therapy in the treatment of partial-onset seizures with or without secondary generalisation in patients with epilepsy aged 16 years and older.

The European Medicines Agency (EMA) has recommended that Vimpat 15 mg/ml syrup should no longer be marketed. The product was voluntarily recalled in September 2011 because of a quality defect in some batches leading to uneven distribution of the active substance in the syrup. As this issue could not be resolved, it was concluded that the benefit of Vimpat 15 mg/ml syrup does not outweigh the risk that patients might receive either too much or too little of the active substance, and therefore it will be discontinued. The film-coated tablet and solution for intravenous use presentations will remain available. An application for a marketing authorisation for a 10 mg/ml formulation was submitted in August 2011 and is currently under review.

Advice to Healthcare Professionals and Key Message

- Doctors should contact patients currently on Vimpat syrup as soon as possible to switch them to Vimpat film-coated tablets whenever possible.
- For patients who cannot take tablets, it may be possible to obtain the United States-approved Vimpat 10 mg/ml liquid formulation, which was not affected by this issue, on a named patient basis. Otherwise, alternative anti-epileptic treatments may have to be considered.
- Pharmacists should return any bottles of Vimpat 15 mg/ml syrup to their supplier.
- Patients should be advised not to stop taking their current medication or change their dose without speaking to their doctor.

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

Product	Safety Issue
Revatio (sildenafil citrate)	Increased risk of mortality in paediatric patients with pulmonary arterial hypertension with the use of higher than recommended doses of Revatio
Multaq (dronedarone)	Restriction of use and new monitoring requirements
Vimpat (lacosamide) 15mg/ml syrup	Product recall due to quality defect
MabThera (rituximab)	Information on fatal infusion related reactions in patient treated for Rheumatoid Arthritis
Sprycel (dasatinib)	Potential risk of pre-capillary pulmonary arterial hypertension
OTC paediatric cough and cold medicines	New recommendations for use in young children
Nplate (Romiplostim)	Risk of disease progression to Acute Myelogenous Leukaemia (AML) with romiplostim use in patients with Myelodysplastic Syndrome