IRISH MEDICINES BOARD

Drug Safety NEWSLETTER

53RD EDITION

Changes to Arrangements for Drug Safety Newsletter Distribution

In the context of expanding use of electronic media to facilitate prompt and efficient notification of important safety information related to the use of medicines, the IMB intends to discontinue provision and distribution of hard copy versions of the Drug Safety Newsletter (DSN) by post over the coming months and to disseminate it through electronic methods only. This is considered an important and appropriate initiative in the context of increasing use of electronic media and the increased focus on transparency and communication arising from the provisions of the revised pharmacovigilance legislation, which came into effect in July 2012. These provisions include the prompt publication of reviews and recommendations undertaken at EU level by the newly established scientific committee, which is known as the Pharmacovigilance Risk Assessment Committee or PRAC. Further information describing the work of the PRAC is included on page 2.

The electronic version of the DSN is in PDF format, thus allowing you to save the newsletter and/or print specific pages. The online version also contains hyperlinks to product information and other documents on the IMB and EMA websites.

To facilitate healthcare professionals, this change in arrangements will be phased in, to allow for provision of email contact details to the IMB and/or registration as a subscriber to the IMB website to receive alerts. It is intended however that by the end of 2013, hard-copy versions of the DSN will no longer be printed and posted. In the meantime, to ensure that you can continue to receive the DSN, healthcare professionals are requested to:

- Register with the IMB to receive an email alert notifying you that future editions of the newsletter This may be done by logging on to the IMB website (**www.imb.ie**) and clicking on to the panel 'Subscribe to our Updates' on the homepage and following the links.
- Ensure that you are on the IMB mailing list for electronic distribution of the DSN. To do so, please submit your email address to **imbpharmacovigilance@imb.ie** or telephone 01 – 6764971 and ask for the pharmacovigilance section to provide your email details, before Monday 30th September 2013

The Pharmaceutical Society of Ireland (PSI) will continue to distribute the DSN to their members as at present and the IMB is liaising with some of the other relevant, professional bodies in Ireland to support additional publication/distribution via their networks. During the interim phase of change over to full electronic distribution, hard-copy versions of the DSN following its publication on the website will continue to be made available.

Key Message

- **Hard copy versions of the IMB Drug Safety Newsletter (DSN) will be phased out over the coming months, when electronic versions will become the main method of dissemination.**
- **Healthcare professionals must register as subscribers to the IMB website, or provide their email contact details by 30th September 2013 to continue to receive the IMB Drug Safety Newsletter.**

In this edition

The Pharmacovigilance Risk Assessment Committee (PRAC)

In the 50th edition of the IMB Drug Safety Newsletter outlining the provisions of the revised pharmacovigilance legislation, a brief overview of the establishment of the new scientific committee at the European Medicines Agency, the Pharmacovigilance Risk Assessment Committee (PRAC), was included.

The mandate of the PRAC covers all aspects of the risk management of the use of medicinal products including the detection, assessment, minimisation and communication relating to the risk of adverse reactions, having due regard to the therapeutic effect of the medicinal product, the design and evaluation of post-authorisation safety studies and pharmacovigilance audit. Regulatory actions that can be taken to minimise risk and maximise the benefits of medicines for patients may include changes to warnings in the product information, restricting the indications for use of a medicine, or in rare circumstances, removal of the medicine from the market, if the risks of a medicine are found to outweigh the benefits (**http://www.ema.europa.eu/ema/index.jsp?curl=pages/about_us/general/general_content_000537.jsp&mid=WC0b01ac058058cb18**).

The PRAC meets on a monthly basis to discuss these issues of risk management of medicines for human use and is responsible for providing recommendations to other relevant EMA Committees, including the Committee for Medicinal Products for Human Use (CHMP) and the Co-ordination group for Mutual Recognition and Decentralised Procedures for human products (CMDh) on any question relating to pharmacovigilance activities in respect of medicinal products for human use. Taking the recommendations of the PRAC into account, these Committees adopt a final scientific opinion that is legally binding. In addition the PRAC is also responsible for providing advice either to the EMA Secretariat, Management Board and European Commission, as applicable.

In the interest of transparency, agendas and adopted minutes of the PRAC meetings are made available to the public on the EMA and IMB websites when finalised, while immediate, high-level outcomes from PRAC are published once meetings are over. Final PRAC recommendations are now highlighted by the IMB on its website, with a link to relevant publications, when available. Information on reviews undertaken by the PRAC, together with recommendations on the outcome of these reviews and implementation of regulatory action may also be reflected in IMB Drug Safety Newsletter (DSN) articles, as appropriate.

Membership of the PRAC includes a representative from each competent authority across the Member States, as well as from patient organisations, healthcare professionals, and independent experts appointed by the European Commission. The Irish PRAC Member, Dr. Almath Spooner is the current Vice-Chair of the Committee for a three year period.

During the March 2013 PRAC meeting, the Committee welcomed the appointment by the European Commission of one member and alternate each representing healthcare-professional and patient organisations. Further information on these appointments is available from the EMA website (**http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2013/03/news_detail_001732.jsp&mid=WC0b01ac058004d5c1**).

Medicines Subject to Additional Monitoring Requirements – Update

Information on the introduction of additional monitoring requirements for certain medicinal products for which there may be limited data/experience (e.g. with long term use), to support prompt identification of any new safety hazards and to allow appropriate regulatory action to be initiated promptly was provided in the 50th edition of the IMB Drug Safety Newsletter (DSN) (**http://www.imb.ie/images/uploaded/documents/DSN%2050%20Final%20version%20for%20web.pdf**). It was noted at that time that the initial list of medicines subject to additional monitoring requirements and the symbol identifying them would be communicated when finalised and approved at EU level. These steps have now been completed and information on the symbol and the initial list of medicines under additional monitoring is now publically available from the EMA website (**http://www.ema.europa.eu/ema/**). The European Medicines Agency (EMA) first published this list on 25th April 2013, and it will be reviewed and updated, as necessary, following consideration by the Pharmacovigilance Risk Assessment Committee (PRAC) at its monthly meetings.

A medicine will be subject to additional monitoring requirements in the following circumstances:

- It contains a new active substance authorised in the EU after 1 January 2011.
- It is a biological medicine, such as a vaccine or a medicine derived from plasma for which there is limited post-marketing experience.
- It has been given a conditional approval, or has been approved under exceptional circumstances.
- The company that markets the medicine is required to carry out additional studies, for instance, to provide more data on long-term use of the medicine or on a rare side effect seen during clinical trials.

Other medicines may also be subject to additional monitoring requirements, based on a decision by the PRAC. A medicine may be added to the list when first approved or at any time during its life cycle. It is intended that medicines will remain on the additional monitoring list for a five year period, or until the PRAC decide to remove it from the list.

The product information for medicines subject to additional monitoring requirements will have a black inverted triangle accompanied by an explanatory statement displayed both in the Summary of Product Characteristics (SPC) and Package leaflet (PL):

▼ This medicinal product is subject to additional monitoring

This symbol will be used in all EU member states to identify medicines under additional monitoring and will start appearing in the product information of the medicines concerned from the autumn of 2013. It is important to note that there may be a delay between the decision to add or remove a medicine from the list and the time when the updated product information becomes available because of the time needed for new supplies of the product information for the medicines concerned to become available on the market.

In addition to these additional monitoring requirements, information on how to report suspected adverse reactions will also be included in the product information for all medicines. Healthcare professionals and patients are particularly encouraged to report any suspected adverse reactions associated with use of medicines subject to additional monitoring requirements, so that any new emerging information can be promptly identified and analysed efficiently.

Key Message:

- **The EMA published the initial list of medicines subject to additional monitoring requirements in April 2013. The list is available on the EMA website (http://www.ema.europa.eu/ema/).**
- **Products subject to additional monitoring will be identifiable by an inverted black triangle accompanied by an explanatory statement in SPCs and PLs.**
- **Please report all suspected adverse reactions to products which carry this symbol.**

Metoject solution for injection, pre-filled syringes – caution in use

Healthcare professionals will be aware that there have been on-going issues with the supply of Metoject 10mg/ml Solution for Injection, pre-filled syringe in Ireland over the last few months and in order to maintain supply, the marketing authorisation holder and distributor (Medac and Fannin healthcare respectively) has imported Metoject 50mg/ml Solution for Injection, pre-filled syringe presentations from the UK and Finland.

These imported products have a significantly higher concentration than the previously available 10mg/ml product. (i.e. five times higher concentration) and healthcare professionals are advised to pay particular attention to the total content of methotrexate in the total volume of the syringe presentations currently available (please see below).

Presentation	**10mg** / 0.2ml	**15mg** / 0.3ml	**20mg** / 0.4ml	**25mg** / 0.5ml
Strength per ml	50mg/ml	50mg/ml	50mg/ml	50mg/ml
Total Syringe Volume	0.20 ml	0.30 ml	0.40 ml	0.50 ml
Methotrexate Content in Syringe volume	**10mg in 0.2ml**	**15mg in 0.3ml**	**20mg in 0.4ml**	**25mg in 0.5ml**

The IMB has requested that a Caution-in-Use Notification (CIUN) is supplied with the product and should be attached to each pack when dispensed. A recent advisory letter from the company was also electronically distributed to pharmacists via the Pharmaceutical Society of Ireland (PSI) at the end of March 2013.

Healthcare professionals are advised to exercise extreme caution when dispensing and administering this higher concentration product, in order to avoid medication errors and potential harm to patients. Metoject should be administered as a **once weekly dose only**. The patient and/or carers should be informed of the risks associated with overdose and the need to adhere to once weekly dosing. It is also suggested that the day of injection should be specified on the prescription and the dispensing label.

Key Message

- **Metoject 50mg/ml Solution for Injection, prefilled syringe is the only Metoject presentation available in Ireland at present.**
- **Metoject 50mg/ml Solution for Injection, prefilled syringe has five times higher concentration that the previously available Metoject 10mg/ml Solution for Injection, prefilled syringe.**
- **Please pay particular attention when dispensing/administering these products to reduce the risk of medication error and potential harm to patients**

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

Product	Safety Issue
Increlex (Mecasermin) http://www.imb.ie/images/uploaded/documents/FINAL%20Increlex%20DHPC.pdf	Communication on the interruption to supply.
Fastum Gel (Ketoprofen) http://www.imb.ie/images/uploaded/documents/FastumGelDHPCMay2013.pdf	Communication on risk minimisation measures for Ketoprofen-containing topical formulations.
Thalidomide Celgene (Thalidomide) http://www.imb.ie/images/uploaded/documents/Thalidomide%20DHCP%20Letter_For%20HCPs_Ire_Final%20v4_05Apr13.pdf	Communication on the risk of haematological second primary malignancies in patients treated with thalidomide.
MabThera (Rituximab) http://www.imb.ie/images/uploaded/documents/MabThera%20DHPC%20Letter%20FINAL.pdf	Communication on the association of MabThera (Rituximab) with Toxic Epidermal Necrolysis and Stevens-Johnson-Syndrome
Incivo (Telaprevir) http://www.imb.ie/images/uploaded/documents/IRE-Incivo-%20FINAL%2008-April-13-.pdf	Management of severe cutaneous adverse reactions (SCAR) with Incivo (telaprevir).
Mimpara (Cinacalet) http://www.imb.ie/images/uploaded/documents/Mimpara-DHCP-IRELAND.PDF	Report of a fatal case with severe hypocalcaemia in a paediatric investigational study.
Nulojix (Belatacept) http://www.imb.ie/images/uploaded/documents/BMS-Nulojix%20DHCP%20Letter%20-14th%20March%202013.pdf	Increased risk of acute graft rejection with Nulojix (belatacept) associated with rapid corticosteroid taper in patients at high immunological risk for acute rejection.
Vistide (Cidofovir) http://www.imb.ie/images/uploaded/documents/Ireland%20DHPC%20Vistide%20(Cidofovir)%2075%20mgml%20concentrate%20for%20solution%20for%20infusion.pdf	Shortage in commercial supply due to product recall following a manufacturing problem.
NeuroBloc (Botulinium Toxin Type B) http://www.imb.ie/images/uploaded/documents/Eisai%20Ltd%20NeuroBloc%20DHPC_Ireland.pdf	Communication on the risks associated with off-label use.
Prolia (Denosumab) http://www.imb.ie/images/uploaded/documents/Prolia-EU%20DHCP%20FINAL_IRELAND.pdf	Communication on the risk of atypical femoral fracture with Prolia.