AUGUST 2016

HPRA DRUG SAFETY NEWSLETTER

76TH EDITION

In this Edition

Valproate-containing medicines - Additional educational materials available for healthcare professionals and patients

The outcome of the Europe-wide review of valproate-containing medicines was communicated to healthcare professionals in December 2014 via the HPRA Drug Safety Newsletter (Edition 65) and a Direct Healthcare Professional Communication (DHPC) circulated by the Marketing Authorisation Holder (MAH) following approval by the HPRA. This review recommended strengthening of restrictions for use of valproate and further characterising the risk of birth defects and developmental disorders in the product information (Summary of Product Characteristics (SmPC) and Package Leaflet (PL)).

In May 2015, educational materials were made available by the MAH (following HPRA approval) as part of the risk minimisation measures developed to inform healthcare professionals and patients about the risks associated with use of valproate by females of child-bearing potential and during pregnancy.

These educational materials have now been updated and enhanced to further support awareness and to facilitate discussion of the risks between healthcare professionals and patients. The additional educational materials include the following:

Booklet for Healthcare Professionals

- This booklet provides up to date information about the risk of neurodevelopmental disorders in children of women who have taken valproate during pregnancy, in addition to the known risk of congenital malformations in exposed babies.
- It also provides points to consider and steps to take when deciding to treat women of child-bearing potential with valproate.
- The booklet should be used in conjunction with the patient guide and checklist, as well as the complete Summary of Product Characteristics (SmPC).

Valproate Patient Guide

- This booklet includes information for all females taking any medicine containing valproate.
- Healthcare professionals should ensure that female patients treated with valproate are provided with the valproate patient guide and that they understand the information it contains. If a patient is a young girl, the guide should be explained to her parent/carer.

Valproate Patient Card

- Pharmacists are requested to distribute a valproate patient card whenever a valproate-containing medicine is dispensed to a female of child-bearing age, unless she confirms that she already has one.
- The pharmacist should encourage the patient to read the patient guide and card together, to understand the information provided and enter her name and date on the card to indicate she has read and understood the information.

Kevin O'Malley House, Earlsfort Centre, Earlsfort Terrace, Dublin 2, Ireland.
T: +353 1 676 4971 E: medsafety@hpra.ie www.hpra.ie

Checklist for Prescribers

- If a prescribing doctor concludes it is necessary to treat, or to continue treating a woman of child-bearing age with a valproate-containing medicine, then the checklist should be used to ensure that all necessary information has been provided to the patient and/or carer and that they fully understand it.

These updated materials have been recently distributed to doctors and pharmacists by the MAH with an accompanying DHPC. The educational materials are also available from the HPRA website.

Advice to Healthcare Professionals

- Valproate should not be prescribed to female children, female adolescents, women of child-bearing potential or pregnant women unless other treatments are ineffective or not tolerated.
- Children exposed in utero to valproate are at a high risk of serious developmental disorders (in up to 30-40% of cases) and/or congenital malformations (in approximately 10% of cases).
- Valproate treatment should only be commenced and supervised by a doctor experienced in managing epilepsy or bipolar disorder.
- Before initiating treatment, the balance of the benefits of treatment with valproate must be weighed against the risks. This should also be considered at routine treatment reviews, when a female reaches puberty and when a woman plans a pregnancy or becomes pregnant. The prescribing doctor should consult the booklet for healthcare professionals.
- All female patients must be informed of and understand the risks associated with valproate during pregnancy and the steps to take if pregnancy occurs or is planned. The valproate patient guide and patient card should be provided to all female patients of child-bearing age and discussed with them to ensure full understanding of the associated risks.
- The prescribing doctor should also use the checklist available to ensure that all necessary information has been provided to the patient and/or carer.
- Further updates will be made to the outer packaging for all valproate-containing products to include a warning for women on the risk of adverse pregnancy outcomes.
- All suspected adverse reactions associated with valproate-containing medicines should be reported to the HPRA via the usual methods (www.hpra.ie).

Key Message

Valproate-containing medicines should not be prescribed to female children, female adolescents, women of childbearing potential or pregnant women, unless other treatments are ineffective or not tolerated, due to the risk of serious developmental disorders and/or congenital malformations.

To further improve awareness of the risks associated with use of valproate-containing medicines in females of child-bearing potential and in pregnancy, updated educational materials and patient alert cards are available and should be used by healthcare professionals to support appropriate and safe prescribing/dispensing of valproate-containing medicines, and by patients/carers to increase their knowledge of these risks.

**Further details on valproate-containing medicines are available at www.hpra.ie*

Miconazole and warfarin - Reminder of the potential for interaction

Miconazole is known to enhance the anticoagulant effect of warfarin and reports of significant bleeding episodes associated with concomitant use of these medicines have been well documented in the literature and spontaneously notified to medicines agencies, including the HPRA. The currently approved Summary of Product Characteristics (SmPC) for Daktarin Oral Gel warns that because miconazole inhibits CYP2C9, caution should be exercised in patients on oral anticoagulants, such as warfarin, and the anticoagulant effect monitored (warfarin dose reduction may be needed). The Package Leaflets (PL) for miconazole products advises users to tell their doctor or pharmacist if they are taking warfarin.

In the context of continuing submission of reports of raised international normalised ratio (INR) resulting in haemorrhage when miconazole and warfarin are used concomitantly, healthcare professionals are reminded of the following recommendations.

Kevin O'Malley House, Earlsfort Centre, Earlsfort Terrace, Dublin 2, Ireland.
T: +353 1 676 4971 E: medsafety@hpra.ie www.hpra.ie

Advice to Healthcare Professionals

- All miconazole products, including those available as over the counter (OTC) medicines (e.g. creams, powders and oral gels) may enhance the anticoagulant effect of warfarin. If miconazole and warfarin are used concurrently, the anticoagulant effect should be carefully monitored and, if necessary, the dose of warfarin reduced.
- Patients should be advised to tell their doctor or pharmacist if they are receiving warfarin before using medicines that contain miconazole (including OTC products).
- Patients should also be advised to seek medical advice immediately if they observe signs of over-anticoagulation during treatment such as sudden unexplained bruising, nosebleeds or haematuria.

Key Message

Reports of clinically significant increases in INR due to interaction between miconazole (including OTC medicines) and warfarin have been received by the HPRA.

If patients are taking miconazole and warfarin concurrently, the anticoagulant effect should be monitored and the warfarin dose reduced, if necessary.

Patients should be advised to read the package leaflet that accompanies all medicines, including OTC medicines, and should tell their doctor and pharmacist if they are receiving warfarin before using any products that contain miconazole.

**Further information on miconazole-containing products is available from www.hpra.ie*

Levonorgestrel-releasing intrauterine devices - Recommendation to prescribe by brand name

A levonorgestrel-releasing intrauterine device (IUD) has been available in Ireland under the brand name Mirena for a number of years, with additional products Jaydess and Levosert authorised more recently, To date however, only two of these products (Mirena and Jaydess) are currently marketed for use in Ireland and it is recommended that they should always be prescribed by brand name because the different products available have different indications and different durations of use.

Mirena
Contains 52mg of Levonorgestrel

Licensed for use for up to 5 years for contraception, idiopathic menorrhagia and protection from endometrial hyperplasia during oestrogen replacement therapy.

Jaydess
Contains 13.5mg of Levonorgestrel

Licensed for use for up to 3 years for contraception.

It is strongly recommended that both Mirena and Jaydess should only be inserted by physicians/healthcare professionals who are experienced in their insertion and/or have undergone sufficient training.

The Marketing Authorisation Holder (MAH) for Jaydess and Mirena (Bayer Healthcare Ltd) has produced information, approved by the HPRA, for prescribers to highlight the differences between Jaydess and Mirena. Apart from being authorised for more indications, Mirena differs from Jaydess in its appearance. Both IUDs are T-shaped levonorgestel releasing devices that are placed within the uterine cavity. However Jaydess contains a silver ring that is identifiable on an ultrasound therefore distinguishing it from Mirena. Information distinguishing the products is available for Jaydess under the educational materials tab on the HPRA website.

Key Message

Two levonorgestrel-releasing intrauterine devices (IUDs) are currently available on the Irish market (Mirena and Jaydess). Both products are indicated for contraception however, Mirena has additional approved indications as well as a longer duration of action.

These products should always be prescribed by brand name and inserted by healthcare professionals experienced in their insertion following sufficient training.

Information highlighting the differences between Jaydess and Mirena was developed by the MAH and is available from the HPRA website.

**Further information on levonorgestrel-releasing IUDs is available from www.hpra.ie*

Kevin O'Malley House, Earlsfort Centre, Earlsfort Terrace, Dublin 2, Ireland.
T: +353 1 676 4971 E: medsafety@hpra.ie www.hpra.ie

Implanon NXT - Risk of device migration in vasculature and lung

Implanon NXT 68mg is a radiopaque, non-biodegradable progestogen only flexible implant for subdermal use (containing the active substance etonogestrel), which is authorised in Ireland since 2010 for contraception. It is strongly recommended that Implanon NXT should only be inserted and removed by healthcare professionals (HCPs) who have completed training in the use of the applicator and techniques for insertion and removal, and, where appropriate, that supervision be requested prior to inserting or removing the implant.

There have been reports of migration of the implant within the arm from the insertion site, which may be related to deep insertion or external forces (e.g. manipulation or contact sports). There have also been rare post-marketing reports of etonogestrel implants (non-radiopaque and radiopaque) located within the vessels of the arm and the pulmonary artery, which may be related to deep insertions or intravascular insertions. Following a review of relevant data from global sources, the product information (Summary of Product Characteristics (SmPC) and Package Leaflet (PL)) for Implanon NXT has been updated to highlight this risk and to inform healthcare providers and patients about the potential consequences and possible actions to take should intravascular migration occur, as well as providing updated instructions for insertion in order to further minimise this risk.

Advice to Healthcare Professionals

- An implant should only be inserted subdermally and by a healthcare professional that has been appropriately trained.
- Insertion, localisation and removal should closely adhere to the detailed guidance and recommendations described in the SmPC.
- Immediately after insertion, the presence of the implant should be verified by palpation.
- The patient should be advised that if the implant cannot be palpated immediately after insertion, or at any time, she should be advised to return to the healthcare professional who inserted the implant immediately.
- If the implant cannot be found in the arm after comprehensive localisation attempts, consideration should be given to applying imaging techniques to the chest.
- In cases where the implant has migrated to the pulmonary artery, endovascular or surgical procedures may be needed for removal.
- As part of its risk minimisation activities to support the safe and effective use of Implanon NXT, the Marketing Authorisation Holder (MAH) has updated their Clinical Training Programme providing a framework to offer practical and consistent guidance and training on Implanon NXT insertion, localisation and removal to all interested healthcare professionals. The MAH has also been requested to bring this information to the attention of healthcare professionals who have already participated in training programmes.
- A Direct Healthcare Professional Communication (DHPC) was circulated by the MAH to relevant healthcare professionals in May 2016 to highlight these updates.

Key Message

There have been rare reports of Implanon NXT implants reaching the lung via the pulmonary artery.

An implant that cannot be palpated at its insertion site in the arm should be located as soon as possible and removed at the earliest opportunity.

The product information (SmPC and PL) for Implanon NXT has been updated to reflect this information and a DHPC was circulated to healthcare professionals in May 2016.

The MAH is currently updating their Clinical Training Programme for healthcare professionals. Healthcare professionals who have previously been trained will have the option to re-train.

**Further details on Implanon NXT are available at www.hpra.ie*

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

PRODUCT	SAFETY ISSUE
Implanon NXT	Risk of migration with Implanon NXT and updated recommendations on insertion, localisation and removal.
Thalidomide Celgene	New important advice regarding viral reactivation and pulmonary hypertension.
Adempas (riociguat)	New contraindication in patients with pulmonary hypertension associated with idiopathic interstitial pneumonias (PH-IIP).
Noxafil (posaconazole)	Noxafil (posaconazole) tablets and oral suspension are not interchangeable.