DECEMBER 2016

HPRA DRUG SAFETY NEWSLETTER

78TH EDITION

In this Edition

Otezla (apremilast) – Important advice regarding suicidal ideation and behaviour

Apremilast is a selective immunosuppressant medicine indicated for use alone or in combination with disease modifying antirheumatic drugs (DMARDs) for the treatment of active psoriatic arthritis in adult patients who have had an inadequate response, or who have been intolerant to DMARD therapy previously. It is also indicated for the treatment of moderate to severe chronic plaque psoriasis in adult patients who failed to respond to, or who have a contraindication to, or are intolerant to other systematic therapy including cyclosporine, methotrexate and ultraviolet-A light (PUVA).

It is important to note that suicidal behaviour-related events and depression are considered to occur more commonly in patients with psoriasis and psoriatic arthritis than in the general population. However, following a recent, thorough regulatory review of this issue, evidence from clinical trials and post-marketing experience suggests a causal association between suicidal ideation and behaviour with the use of apremilast.

Advice to Healthcare Professionals

- Suicidal ideation and behaviour have been reported from clinical trials and post-marketing experience (with or without a history of depression) with a frequency of uncommon (≥1/1000 to ≤1/100), while cases of completed suicide were reported during the post marketing period in patients taking apremilast.
- The balance of benefits and risks of treatment with apremilast should be carefully considered in patients with a history of psychiatric symptoms or patients taking medicines which are likely to cause psychiatric symptoms.
- Treatment with apremilast should be discontinued in patients who present with new or worsening psychiatric symptoms, or if suicidal ideation/suicidal behaviour is identified.
- Patients and carers should be informed of these risks and advised to contact the prescriber if any changes in mood or behaviour occur or in the case of any signs of suicidal ideation.
- The product information (Summary of Product Characteristics (SmPC) and Package Leaflet (PL)) for apremilast will be updated shortly.

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Key Message

Following a regulatory review, evidence from clinical trials along with post-marketing experience suggests a causal association between suicidal ideation and behaviour with the use of apremilast.

It is therefore recommended that the risks and benefits of commencing or continuing treatment with apremilast should be carefully assessed in patients with previous or existing psychiatric symptoms or if concomitant treatment with other medicinal products that are known to cause psychiatric effects.

Patients and carers should be fully informed of these risks and advised to contact their doctor if symptoms emerge.

All suspected adverse reactions associated with apremilast should be reported to the HPRA via the various reporting methods available (www.hpra.ie)

* *Further information on apremilast is available from www.hpra.ie and www.ema.europa.eu*

Lenalidomide (Revlimid) – Advice regarding viral reactivation

Lenalidomide (Revlimid) is an immunomodulatory agent similar to thalidomide and has antineoplastic, antiangiogenic and proerythropoietic properties. It is authorised for the treatment of adult patients with previously untreated multiple myeloma that are not eligible for transplant or in combination with dexamethasone in patients who have received at least one previous treatment. Lenalidomide is also indicated for the treatment of myelodysplastic syndromes and in patients with relapsed or refractory mantle cell lymphoma.

Viral reactivation, including herpes zoster and hepatitis B viruses (HBV), has been reported in the context of post marketing monitoring of lenalidomide. Cases of hepatitis B reactivation have been reported across the EU very rarely (<1/10,000), but four cases did progress to hepatic failure. In these four cases, lenalidomide was discontinued and the patients required antiviral treatment. Previously infected patients should be closely monitored throughout therapy for signs and symptoms of viral reactivation, including active HBV infection.

Reactivation of herpes zoster led in some cases, to disseminated herpes zoster, meningitis herpes zoster or ophthalmic herpes zoster necessitating antiviral treatment and the permanent discontinuation or temporary discontinuation of treatment with lenalidomide.

Patients treated with lenalidomide usually have pre-existing risk factors for viral reactivation, including underlying progressive disease, older age and prior or concomitant treatment with immunosuppressive treatments including stem cell transplant. The immunosuppressive effect of lenalidomide may further increase the risk of viral reactivation in these previously infected patients.

Advice to Healthcare Professionals

- Cases of viral reactivation have been reported in patients treated with lenalidomide particularly in patients previously infected with herpes zoster or HBV.
- HBV status should be established before initiating treatment with lenalidomide.
- A doctor with expertise in the treatment of hepatitis B should be consulted for patients who test positive for HBV infection.
- Previously infected patients should be closely monitored for signs and symptoms of viral reactivation, including active HBV infection, throughout therapy.

Key Message

There have been very rare reports of viral reactivation following treatment with lenalidomide. This has occurred particularly in patients previously infected with herpes zoster or hepatitis B viruses (HBV).

Previously infected patients should be closely monitored throughout treatment with lenalidomide for signs and symptoms of viral reactivation.

Pre-existing risk factors for viral reactivation include old age, an underlying progressive condition and prior or concomitant treatment with immunosuppressive treatments.

All suspected adverse reactions associated with lenalidomide should be reported to the HPRA via the various reporting methods available (www.hpra.ie)

* *Further information on lenalidomide is available from www.hpra.ie and www.ema.europa.eu*

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Levetiracetam 100mg/ml Oral Solution - Global reports of medication errors resulting in the administration of higher than intended doses of levetiracetam

The European Medicines Agency's (EMA) Pharmacovigilance Risk Assessment Committee (PRAC) recently completed a review of global reports of medication errors with levetiracetam oral solution, including case reports of an up to 10-fold accidental overdose. The majority of cases occurred in children aged between 6 months and 11 years and where information could be retrieved from reports, the use of an inadequate dosing device (e.g. confusion between a 1 ml and a 10 ml syringe) was identified as an important cause. Another identified cause was the misunderstanding of the caregiver about how to properly measure the dose.

In Ireland, levetiracetam is currently available in a number of different presentations, including tablets, solution for infusion and oral solution. The oral solution, authorised across the European Union since 2003, is approved for use, as monotherapy and adjunctive therapy in various forms of epilepsy in paediatric and adult patients.

Advice to Healthcare Professionals

- Physicians should always prescribe the dose in mg with ml equivalence based on the correct age.
- Physicians should prescribe the recommended presentation of levetiracetam oral solution with the appropriate syringe according to the age/bodyweight of the patient.
- Pharmacists should ensure the correct syringe is dispensed with the corresponding presentation:
  - 150 ml bottle with 1 ml syringe for infants from 1 month to less than 6 months;
  - 150ml bottle with 3ml syringe for children 6 months to less than 4 years and below 50kg bodyweight;
  - 300 ml bottle with 10ml syringe for children 4 years and older and below 50 kg bodyweight;
  - 300ml bottle with 10 ml syringe for children, adolescents and adults with 50kg and more bodyweight.
- With each prescription, physicians and pharmacists should advise the patient/carer on how to measure the correct dose.
- Patients/carers should also be reminded frequently that only the syringe provided with the medicine should be used. Once the bottle is empty, the empty syringe should be discarded and not kept.
- The package leaflet and outer carton will be updated to improve clarity.
- The MAH for the brand Keppra circulated a Direct Healthcare Professional Communication (DHPC) (following approval by the HPRA) on this topic in November 2016.
- Healthcare professionals are reminded to report any medication errors associated with overdose to the HPRA Pharmacovigilance Department using the usual methods (www.hpra.ie).

Key Message

Cases of an up to 10-fold accidental overdose with levetiracetam oral solution have been reported, the majority of which occurred in children aged between 6 months and 11 years.

Doctors should always prescribe the dose in milligrams with millilitre equivalence based on the correct age.

Pharmacists should ensure the appropriate presentation of the oral solution is dispensed.

With every prescription and every dispensing, the doctor and pharmacist should advise the patient/caregiver on how to measure the prescribed dose.

All suspected adverse reactions associated with levetiracetam oral solution should be reported to the HPRA via the various reporting methods available (www.hpra.ie)

* *Further information on levetiracetam-containing products including Keppra is available from www.hpra.ie and www.ema.europa.eu*

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Improved Access to Educational Materials on the HPRA website

The HPRA previously highlighted the publication of HPRA approved educational materials for medicines on its website in the 73rd edition of the Drug Safety Newsletter published in February 2016. Following feedback from stakeholders, these materials have been made more directly and easily accessible from the HPRA website using the 'Find a Medicine' search option on the homepage (www.hpra.ie). For a full list of medicines that have educational materials, the advanced search option (under 'Find a Medicine' on the HPRA homepage) can be used once the box entitled 'Only Medicines with Educational Materials' is checked at the bottom of the page.

Educational materials aim to minimise important risks and maximise the risk-benefit balance of a medicinal product. The content of educational materials aims to supplement the currently authorised product information for the medicinal product in order to support safe and effective prescribing and use. They are designed to fulfil specific risk minimisation objectives and focus on specific safety concern(s) in order to provide clear statements and concise messages describing actions to be taken in order to prevent and minimise these risks. Educational materials are developed by the Marketing Authorisation Holder (MAH) for a medicinal product when specifically recommended by a national competent authority (such as the HPRA) and these must be reviewed and approved by the HPRA prior to distribution to Irish healthcare professionals and patients.

Educational materials may be targeted towards healthcare professionals (e.g. doctors, pharmacists and nursing staff) and/or patients or their carers. Examples of educational materials for healthcare professionals include healthcare professional guides, dosing and administration guides, prescriber checklists and monitoring charts. Examples of educational materials directed at patients include patient alert cards, patient guides and patient reminder cards.

Educational materials and tools are specific to the medicinal product concerned and there may be minor differences between educational materials produced by different MAHs, although their medicinal product may contain the same active substance. However, the core messages relating to risk minimisation will be the same.

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

PRODUCT	SAFETY ISSUE
Keppra (levitiracetam)	Risk of medication errors associated with overdose.
Otezla (apremilast)	New important advice regarding suicidal ideation and behavior.
Revlimid (lenalidomide)	New important information regarding viral reactivation.

Correspondence/Comments should be sent to the Pharmacovigilance Section, Health Products Regulatory Authority, contact details below.

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