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HPRA DRUG SAFETY NEWSLETTER

70TH EDITION

In this Edition

Proton Pump Inhibitors (PPIs) - very rare reports of subacute cutaneous lupus erythematosus (SCLE)

Proton pump inhibitors (PPIs)* are indicated in the treatment of gastric and duodenal ulcers, NSAID associated ulcers, gastro-oesophageal reflux, Zollinger-Ellison syndrome and in combination with antibacterial therapy for eradication of Helicobacter pylori. Some products are indicated for short term use to treat reflux symptoms in adults (see individual SmPCs on www.hpra.ie for full details of licensed indications).

Reports of subacute cutaneous lupus erythematosus (SCLE) in association with PPIs have been reviewed by the European Medicines Agency's (EMA) Pharmacovigilance Risk Assessment Committee (PRAC). The signal of an association was originally triggered by a retrospective medical chart review of patients diagnosed with SCLE over a 19-year period[1]. Overall the cases were well documented with supporting biopsy and serological tests. These cases were supported by a case control study[2] which showed an increased risk of SCLE in patients exposed to PPIs.

Taking into consideration the relevant data across all substances in the class, including some cases with positive re-challenge, the evidence from published literature, and the likelihood of under-reporting given that photosensitivity is a known side effect of PPIs, the PRAC agreed that the product information of medicinal products containing PPIs should be amended to reflect the risk of SCLE.

Advice to Healthcare Professionals

- Proton pump inhibitors are associated with very infrequent cases of SCLE. If lesions occur, especially in sun-exposed areas of the skin, and if accompanied by arthralgia, the patient should be advised to seek medical help promptly and the health care professional should consider stopping the proton pump inhibitor.
- SCLE after previous treatment with a proton pump inhibitor may increase the risk of SCLE with other proton pump inhibitors.
- The product information (Summary of Product Characteristics (SmPC) and Package Leaflet (PL)) for all PPIs (prescription and non-prescription) will be updated to reflect this information.

Key Message

- Proton Pump Inhibitors have been associated with very infrequent cases of SCLE

** The active substances included in this review were omeprazole, esomeprazole, rabeprazole, pantoprazole, lansoprazole and dexlansoprazole. See www.hpra.ie for authorised product names and SmPCs for indications.*

References

1. Sandholt LH, Laurinaviciene R, Bygum A. Proton pump inhibitor-induced subacute cutaneous lupus erythematosus. *Br J Dermatol. 2014;170:342-51*
2. Gronhagen CM, Forced CM, et al. Subacute cutaneous lupus erythematosus and its association with drugs: a population based matched case-control study of 234 patients in Sweden. *Br J Dermatology.* 2012; 167:296-305

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Donepezil - Reports of Rhabdomyolysis

Donepezil* is a specific and reversible inhibitor of acetylcholinesterase which has been authorised in Ireland since 1997 for use for the symptomatic treatment of mild to moderately severe Alzheimers dementia.

Reports of rhabdomyolysis associated with donepezil were recently reviewed by the EMA's Pharmacovigilance Risk Assessment Committee *(PRAC)*. Rhabdomyolysis is a clinical and biochemical syndrome that results from the breakdown of skeletal muscle and the release of intracellular contents into the circulatory system. Rhabdomyolysis can cause serious and sometimes fatal abnormal heart rhythms, kidney damage and kidney failure, but is generally treatable if recognised promptly.

The PRAC considered cases of rhabdomyolysis from post-marketing spontaneous reports and clinical trials. Whilst the individual cases do not provide strong evidence of a causal association between donepezil and rhabdomyolysis, based on the cumulative information from 11 cases in particular, a causal or contributory role for donepezil in these cases of rhabdomyolysis and other less serious muscle disorders including weakness and pain cannot be excluded.

Rhabdomyolysis has been reported to occur independently of Neuroleptic Malignant syndrome (NMS) and in close temporal association with donepezil initiation or dose increase.

Rhabdomyolysis can also be a feature of NMS, a potentially life-threatening condition characterised by hyperthermia, muscle rigidity, autonomic instability, altered consciousness and elevated serum creatine phosphokinase levels. NMS has been reported to occur very rarely in association with donepezil, particularly in patients also receiving concomitant antipsychotics. Additional signs may include myoglobinuria (rhabdomyolysis) and acute renal failure. If a patient develops signs and symptoms indicative of NMS, or presents with unexplained high fever without additional clinical manifestations of NMS, treatment should be discontinued.

Advice to Healthcare Professionals

- Rhabdomyolysis has been reported very rarely in patients treated with donepezil and has occurred independently of NMS and in close temporal association with donepezil initiation or dose increase.
- Patients and carers should be made aware of and advised to immediately report any signs or symptoms of rhabdomyolysis experienced (e.g. muscle weakness, tenderness or pain particularly, if at the same time, they feel unwell, have a high temperature or have dark urine.)
- The product information for donepezil (Summary of Product Characteristics (SmPC) and Package Leaflet (PL)) will be updated accordingly shortly.

Key Message

- Rhabdomyolysis has been reported very rarely in patients treated with donepezil and has occurred independently of NMS and in close temporal association with donepezil initiation or dose increase.
- Patients and carers should be alerted to signs and symptoms of these conditions and told to inform their doctor immediately if any experienced.

** Brands include Aricept, Donesyn, Dozept, Donecept. See www.hpra.ie for further details.*

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Adverse Reaction Reporting during 2014

The HPRA continues to place great emphasis on encouraging and promoting the submission of adverse reaction reports associated with the use of medicines from its stakeholders. These reports are important to highlight potential safety issues from medicines in use and ultimately assist the HPRA in monitoring the safety of medicines on the Irish market.

During 2014, we received a total of 2,884 suspected adverse reaction reports occurring in Ireland from healthcare professionals, members of the public and pharmaceutical companies. A breakdown of the reports by source is outlined below and it is important to note that reports submitted by pharmaceutical companies, will have first been brought to their attention by healthcare professionals, patients and consumers, prior to onward reporting to HPRA.

In keeping with experience in other European countries, reporting rates were highest for newly authorised medicines, with nearly 20% of the reports received associated with the use of medicines subject to additional monitoring requirements. The requirements for additional monitoring introduced in the context of the legislative revisions in 2012 highlighted the importance of reporting all suspected adverse reactions associated with the use of these products, identifiable by an inverted black triangle on the product information (Summary of Product Characteristics (SmPC) and Package Leaflet (PL) and the contribution of reporters in highlighting experience with these new medicines, for which limited data may be available, is especially helpful. Reporting rates may also be influenced by their ease of recognition and may be stimulated by publicity about a particular medicine or reaction.

Breakdown of Reports by Source for 2014

Source of Suspected Adverse Reaction Reports	%
Pharmaceutical company	67
Community Care doctor	7
General Practitioner	4
Hospital Doctor/Specialist	4
Hospital Pharmacist	4
Community Pharmacist	4
Nurse	4
Patient/Consumer	3
Clinical Trial reports	2
Other	1

Individual case reports are followed up by the HPRA, with feedback information provided to reporters, as appropriate. Relevant, anonymised reports (i.e. serious, suspected cases) notified directly to the HPRA by healthcare professionals or members of the public are forwarded to the appropriate marketing authorisation holders (MAHs) and the European Medicines Agency (EMA) within the agreed timeframes and formats. The HPRA also continues to provide details of reports received to the World Health Organisation (WHO) for inclusion on its international database.

There are several options in place for reporting suspected adverse reactions to the HPRA. These are as follows:

- By following the links to the online reporting options accessible from the HPRA homepage (www.hpra.ie)
- Using the downloadable report form also accessible from the HPRA website, which may be completed manually and submitted to the HPRA via 'freepost'
- Using the traditional 'yellow card' report, which also utilises a freepost system
- By telephone to the HPRA Pharmacovigilance section (01-6764971)

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

PRODUCT	SAFETY ISSUE
Mirabegron (Betmiga)	New recommendations about the risk of increase in blood pressure
Denosumab (Xgeva)	Risk of osteonecrosis of the jaw- new contraindication and introduction of a patient reminder card to minimise the risk
Invokana (canagliflozin), Vokanamet (cangliflozin/metformin), Forxiga (dapagliflozin), Xigduo (dapagliflozin/metformin), Jardiance (empagliflozin), Synjardy (empagliflozin/metformin)	Risk of diabetic ketoacidosis during treatment with SGLT2 inhibitors
Ketoconazole	Updated information and monitoring recommendations to minimise the risk of hepatotoxicity

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

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