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HPRA DRUG SAFETY NEWSLETTER

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In this Edition

Quinine – reminder of safety profile and potential drug-drug interactions particularly where used for nocturnal leg cramps

The European Medicines Agency's (EMA) Pharmacovigilance Risk Assessment Committee (PRAC) recently concluded a routine periodic review of medicinal products containing the active substance quinine.

In Ireland, medicinal products containing quinine are licensed as a sulphate salt for the treatment and prevention of nocturnal leg cramps in adults and the elderly (when cramps cause regular disruption of sleep). At higher doses, medicinal products containing quinine are also indicated for the treatment of malignant tertian malaria including chloroquine-resistant malaria.

Having examined the available evidence, the PRAC considered that while the risk-benefit balance of medicinal products containing quinine in both licensed indications remains unchanged, the product information for these medicines should be updated to advise caution in patients predisposed to QT-prolongation, and in patients with atrioventricular block.

Additionally, the EU review recommended that prescribers be reminded of appropriate use of quinine for the treatment and prevention of nocturnal leg cramps. As already described in the product information, patients should have an initial trial of 4 weeks. During this period, patients should be closely monitored for hypersensitivity reactions known to be associated with quinine (for example, thrombocytopenia). Quinine should be discontinued after 4 weeks if there is no benefit. Treatment should be interrupted every 3 months to re-assess continuing need.

Background to the review

Quinine is an isomer of quinidine, a class 1a antiarrythmic which reduces the velocity of cardiac conduction. The product information already advises that quinine should be used with caution in patients with atrial fibrillation or other serious heart disease, and that in excessive doses the QT interval may be prolonged. However, two recent publications (Gjesing et al., 2015, Sheehan et al., 2016) suggest that patients with multiple risk factors for QT-prolongation or atrioventricular block may also be at risk of cardiotoxicity even at therapeutic doses.

Also arising from this routine assessment of the active substance and based on pharmacokinetic data, a warning will be added to product information regarding the potential for quinine to increase levels of phenobarbital and of carbamazepine.

Advice to Healthcare Professionals

- Quinine should be used with caution in patients with conditions which predispose to QT-prolongation and in patients with atrioventricular block.
- Caution is advised when administering quinine with drugs which could prolong the QT interval.
- As described in the product information, when used for the treatment and prevention of nocturnal leg cramps, quinine should be discontinued after the first 4 weeks if there is no benefit. Quinine should be interrupted every 3 months to re-assess continuing need.

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Key Message

Quinine should be used with caution in patients with conditions which predispose to QT-prolongation, in patients with atrioventricular block, or when quinine is co-administered with drugs which could prolong the QT interval.

When used for nocturnal leg cramps, the need for continuing treatment should be re-assessed regularly.

Further details on quinine-containing medicinal products are available on www.hpra.ie.

References

Amabeoku, G., Chikuni, O., Akino, C., and Mutetwa, S. (1993). Pharmacokinetic interaction of single doses of quinine and carbamazepine, phenobarbitone and phenytoin in healthy volunteers. East African Medical Journal, 70(2), pp. 90-93.

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Sheehan, E., Frizzell, J., Gabaldon, J. and West, M. (2016). Quinine and the ABCs of Long QT: A Patient's Misfortune with Arthritis, (Alcoholic) Beverages, and Cramps. Journal of General Internal Medicine, 31(10), pp.1254-1257.

Flucloxacillin and concomitant paracetamol – risk of high anion gap metabolic acidosis in very rare cases

The Pharmacovigilance Risk Assessment Committee (PRAC) of the European Medicines Agency (EMA) recently concluded a review of high anion gap metabolic acidosis (HAGMA) with flucloxacillin and concomitant paracetamol therapy. Flucloxacillin-containing medicinal products are licensed in Ireland under various brand names for the treatment of specified bacterial infections. Evidence in literature and limited spontaneous reports seems to support the possibility of the appearance of a specific type of HAGMA (pyroglutamic acidosis) in the presence of flucloxacillin and paracetamol. Having reviewed the available evidence, the PRAC considered that the product information should be updated accordingly to reflect this risk. In most cases, the interaction is described in patients treated with large doses of paracetamol and after a long period of administration and also in high doses of flucloxacillin.

Advice to Healthcare Professionals

- Flucloxacillin with concomitant paracetamol use has been associated with very rare cases of high anion gap metabolic acidosis.
- Patients with severe renal impairment, sepsis or malnutrition might be at higher risk of experiencing high anion gap metabolic acidosis especially if the maximum daily doses of paracetamol are used.

Key Message

In very rare cases flucloxacillin with concomitant paracetamol use has been associated with cases of high anion gap metabolic acidosis.

The product information (Summary of Product Characteristics (SmPC) and Package Leaflet (PL)) for flucloxacillin-containing medicinal products will be updated to reflect this information.

Flucloxacillin-containing medicinal products include Floxapen, Flucillin, and Geriflox. Further details are available on www.hpra.ie.

Epoetins: new warnings on Severe Cutaneous Adverse Reactions (SCARs)

The Pharmacovigilance Risk Assessment Committee (PRAC) of the European Medicines Agency (EMA) recently completed a detailed analysis of severe cutaneous adverse reactions (SCARs) associated with epoetin-containing medicines. This review was initiated following post-marketing reports of SCARs including Stevens-Johnson syndrome (SJS) and Toxic Epidermal Necrolysis (TEN) with some epoetins. The PRAC concluded that SCARs, including SJS and TEN, are considered a class effect for all epoetins and the product information for these medicines will be updated accordingly.

A Direct Healthcare Professional Communication (DHPC) was circulated to relevant healthcare professionals by the marketing authorisation holders (MAHs) for epoetin-containing medicines detailing the risk of SCARs associated with these medicines.

Human endogenous erythropoietin (EPO) is a growth factor produced primarily by the kidney in response to hypoxia and interacts with erythroid progenitor cells to increase red blood cell (RBC) production. There are several forms of synthetic erythropoietin licensed in Ireland (i.e. darbepoetin alfa, epoetin alfa, epoetin beta, epoetin theta, epoetin zeta and methoxy polyethylene glycol-epoetin beta) under various brand names for specified anaemias e.g. of renal failure or malignancy, or in the case of certain epoetins, for use before autologous blood donation, or for high-risk patients prior to specific surgeries.

Advice to Healthcare Professionals

- Severe cutaneous adverse reactions (SCARs), some life-threatening or fatal, including cases of Stevens-Johnson syndrome (SJS) and Toxic Epidermal Necrolysis (TEN) have been reported in patients treated with epoetins.
- SCARs are considered to be a very rare class effect of all epoetins.
- The reactions have been more severe with long-acting epoetins.
- Patients should be monitored and advised of the signs and symptoms of severe skin reactions when starting treatment with an epoetin product.
- Patients should be instructed to contact their doctor immediately and stop epoetin treatment if they develop:
  - widespread rash with reddening and blistering of the skin and oral mucosa, eyes, nose, throat, or genital area, which follow flu-like symptoms including fever, tiredness, muscle and joint pain.
- Patients who experience SCARs considered to be related to the use of an epoetin should never be re-exposed to an epoetin.

Key Message

Severe cutaneous adverse reactions (SCARs) are considered to be a class effect of all epoetins.

When starting treatment, patients should be closely monitored and advised of the signs and symptoms of severe skin reactions (detailed above).

Patients who develop these signs and symptoms should be instructed to contact their doctor immediately and stop epoetin treatment.

Epoetin-containing medicinal products include Abseamed, Aranesp, Binocrit, Biopoin, Eporatio, Epoetin alfa Hexal, Eprex, Mircera, NeoRecormon, Retacrit, and Silapo. Further details are available on www.hpra.ie or www.ema.europa.eu.

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Adverse reaction reporting during 2016

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 signal potential safety issues from medicines in use and ultimately to assist the HPRA in monitoring the safety of medicines on the Irish market.

During 2016, a total of 3,264 suspected adverse reaction reports were received by the HPRA from healthcare professionals, members of the public and pharmaceutical companies. This represents a 15% increase in overall reporting rates compared with 2015. The breakdown of reports according to their source is outlined in the table below.

Report Source	**%**
Pharmaceutical company	69 *
Patient/Consumer	10
Community Pharmacist	4
General Practitioner	3
Nurse	3
Community Care Doctor	3
Hospital Pharmacist	3
Hospital Doctor/Specialists	2
Healthcare Professional - Other	2
Clinical Trial Reports	1

* *Reports submitted by pharmaceutical companies will have first been brought to their attention by healthcare professionals, patients and consumers, prior to onward reporting to the HPRA.*

In keeping with experience in other European countries, reporting rates were highest for newly authorised medicines. Medicines subject to additional monitoring accounted for 29% of the reports submitted during 2016. The requirements for additional monitoring, introduced in the context of the pharmacovigilance legislative revisions in 2012, highlight the importance of reporting all suspected adverse reactions associated with the use of these products which are identifiable by a black inverted triangle included on the accompanying package leaflet (PL) and the summary of product characteristics (SmPC).

Individual case reports are followed up by the HPRA, with feedback information provided to reporters, as appropriate. Anonymised reports notified directly to the HPRA by healthcare professionals or members of the public are forwarded to the European Medicines Agency's (EMA) Eudravigilance database for inclusion in signal detection activities. Stakeholders, including the World Health Organisation (WHO), marketing authorisation holders, regulatory authorities, academia, healthcare professionals and patients may all access data held in the EudraVigilance database, based on the European Medicines Agency's (EMA) EudraVigilance access policy. This policy is designed to provide as much information as possible to relevant stakeholders, while meeting data protection obligations.

Suspected adverse reactions may be reported to the HPRA in a number of ways:

- By submitting an online adverse reaction report form, accessible from the HPRA homepage (www.hpra.ie);
- By printing and completing a copy of our adverse reaction report form from our website and sending to the HPRA via Freepost, or by downloading and submitting by email to medsafety@hpra.ie;
- By completing a 'Yellow Card' report and sending to the HPRA using Freepost;
- By telephone to the HPRA Pharmacovigilance section (01 676 4971).

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

PRODUCT	**SAFETY ISSUE**
Gilenya (fingolimod)	Contraindications in patients with cardiac conditions.
Human Epoetins	New warnings on severe cutaneous adverse reactions.

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

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