Drug Safety Update

Latest advice for medicines users

The monthly newsletter from the Medicines and Healthcare products Regulatory Agency and its independent advisor the Commission on Human Medicines

Volume 9, Issue 2, **September 2015**

Contents

The Medicines and Healthcare products Regulatory Agency is the government agency which is responsible for ensuring that medicines and medical devices work, and are acceptably safe.

The Commission on Human Medicines gives independent advice to ministers about the safety, quality, and efficacy of medicines. The Commission is supported in its work by Expert Advisory Groups that cover various therapeutic areas of medicine.

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This month, we would like to make you aware that proton pump inhibitors (PPIs) are associated very infrequently with cases of subacute cutaneous lupus erythematosus (SCLE), a non-scarring dermatosis that can develop in sun-exposed areas. If a patient treated with a PPI develops lesions—especially in sun-exposed areas of the skin—and it is possibly accompanied by arthralgia, they should be advised to avoid exposure of the skin to sunlight; SCLE should be considered a possible diagnosis. The PPI should be stopped unless it is imperative for a serious acid-related condition. Furthermore, a patient who develops SCLE with a particular PPI may be at risk of the same reaction with another—see article 1.

If you have not already downloaded the new mobile app for reporting suspected side effects, why not give it a try? Our article this month summarises the app's main features and how we hope to develop it in the future. You can help by sending us your thoughts.

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1 Proton pump inhibitors: very low risk of subacute cutaneous lupus erythematosus

Proton pump inhibitors (PPIs) are associated with very infrequent cases of subacute cutaneous lupus erythematosus (SCLE), a non-scarring dermatosis that can develop in sun-exposed areas.

If a patient treated with a PPI develops lesions—especially in sun-exposed areas of the skin—and it is accompanied by arthralgia:

- Advise them to avoid exposing the skin to sunlight
- Consider SCLE as a possible diagnosis
- Consider stopping use of the PPI unless it is imperative for a serious acid-related condition. A patient who develops SCLE with a particular PPI may be at risk of the same reaction with another
- In most cases, symptoms resolve on PPI withdrawal. Topical or systemic steroids might be necessary for treatment of SCLE only if there are no signs of remission after a few weeks or months

Report any suspected side effect with PPIs, or to any medicine, on a Yellow Card: https://yellowcard.mhra.gov.uk/

Proton pump inhibitors

PPIs reduce the secretion of stomach acid and are widely used medicines for management of acid-related conditions, including: reflux oesophagitis; gastric and duodenal ulcers; and Zollinger-Ellison syndrome. The following PPIs are available in the UK: esomeprazole; lansoprazole; omeprazole; pantoprazole; and rabeprazole Subacute cutaneous lupus erythematosus.

SCLE is characterised by polycyclic erythematous scaly plaques or confluent psoriasiform papulosquamous lesions, which may be accompanied by arthralgia. Skin tests (such as direct immunofluorescence) and serological tests (including presence of antibodies against Ro or Sjögren's-syndrome-related antigen A [SSA]) can be used to diagnose SCLE.

Drug-induced SCLE can occur weeks, months, or even years after exposure to the drug.

Evidence for the association

Considering the extensive use of PPIs, very few cases of SCLE have been reported. Nevertheless, evidence from clinical literature and from cases reported to medicines regulators including via the Yellow Card Scheme supports a causal association between PPIs and SCLE. Product information is being updated to include this advice for healthcare professionals and patients or carers.

A Swedish case-control study that linked a patient register with a prescribed-drug register estimated that the risk of developing SCLE was almost 3 times higher in patients on PPIs compared with that of the general population (odds ratio 2.9 [95% CI: 2.0–4.0]).[1]

A review of medical records of patients at a dermatology unit in a university hospital in Denmark identified 19 cases of SCLE associated with PPIs over 19 years. Of these, 3 cases were classified as definitely caused by a PPI and 14 were classified as probable.[2]

A further 17 cases of SCLE after PPI use have been reported in clinical literature.[3-8]

Cumulatively, of the cases reviewed from literature and from case reports submitted by PPI licence holders to medicines regulators, there have been 36 cases of positive dechallenge (ie, SCLE resolved on stopping PPI) and 4 cases of positive rechallenge (ie, SCLE reoccurred with a different PPI to the one that first triggered the condition).

Article citation: Drug Safety Update volume 9 issue 2 September 2015: 1

1 Grönhagen CM and others. Subacute cutaneous lupus erythematosus and its association with drugs: a population-based matched case-control study of 234 patients in Sweden. Br J Dermatol. 2012; 167: 296–305.
2 Sandholdt LH and others. Proton pump inhibitor-induced subacute cutaneous lupus erythematosus. Br J Dermatol 2014; 170: 342–51.
3 Almebayadh M and others. Subacute cutaneous lupus erythematosus induced and exacerbated by proton pump inhibitors. Dermatology 2013; 226: 119–23.
4 Reich A, Maj J. Subacute cutaneous lupus erythematosus due to proton pump inhibitor intake: case report and literature review. Arch Med Sci 2012; 8: 743–47.
5 McCourt C and others. Anti-Ro and anti-La antibody positive subacute cutaneous lupus erythematosus (SCLE) induced by lansoprazole. Eur J Dermatol 2010; 20: 860–61.
6 Panting KJ et al. Lansoprazole-induced subacute cutaneous lupus erythematosus. Clin Exp Dermatol 2009; 34: 733–34.
7 Dam C, Bygum A. Subacute cutaneous lupus erythematosus induced or exacerbated by proton pump inhibitors. Acta Derm Venereol 2008; 88: 87–89.
8 Bracke A and others. Lansoprazole-induced subacute cutaneous lupus erythematosus: two cases. Acta Derm Venereol 2005; 85: 353–54.

2 Download the Yellow Card mobile app to report suspected adverse drug reactions

On 14 July 2015, the Yellow Card mobile app was launched. Use it to report suspected reactions and receive up to date information on your medicines of interest.

The app, as reported in the July Drug Safety Update, enables you to create a watchlist of medicines of interest that you can track for regular news and alerts, even if you do not have a side effect to report at the time. You can also review Yellow Card records for medicines and vaccines, as well as send your own reports on the move—with an immediate notification that your information has been received.

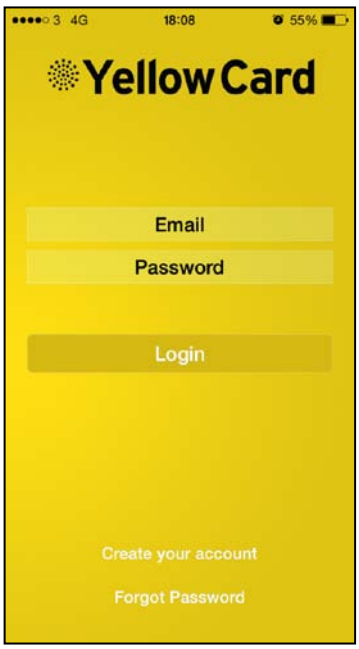
As at the end of August 2015, the app had been downloaded 723 times on Apple devices and 314 times on Android. This has resulted in 27 suspected adverse drug reaction reports being submitted which have contributed to our signal detection activities. Furthermore, some of the most positive feedback we have received is for the app's suspected adverse drug reaction overviews and its news items for relevant products of interest. We are closely following the numbers of suspected adverse drug reactions received via the app and the safety issues identified from these reports. We are also looking at the most common medicines that are being followed by app users via their watchlists to help us understand what news and information is of most interest to users.

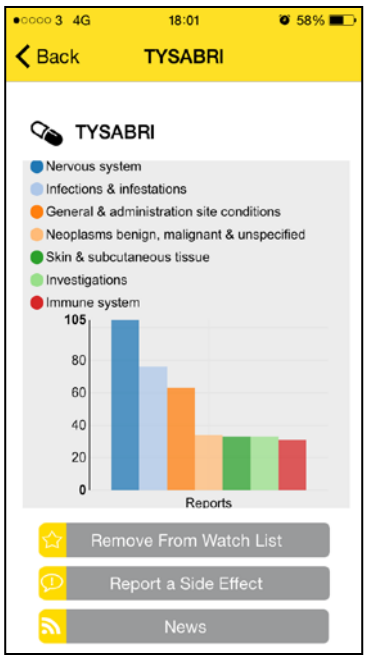
If you have already downloaded the app, why not start building up your watchlist? You can use this to receive information about medicines you frequently prescribe, medicines used in an area in which you specialise, or those that you or a family member are taking.

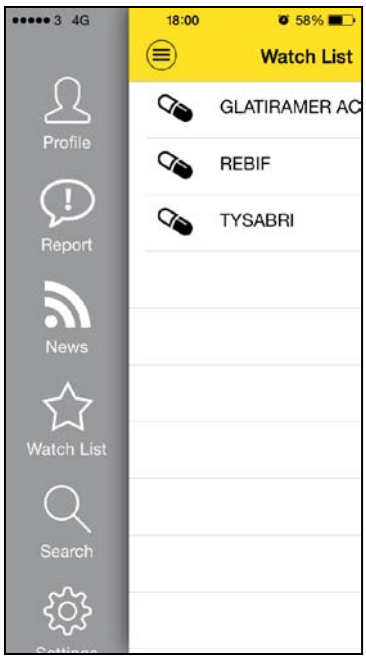
Contact us with your views and suggestions

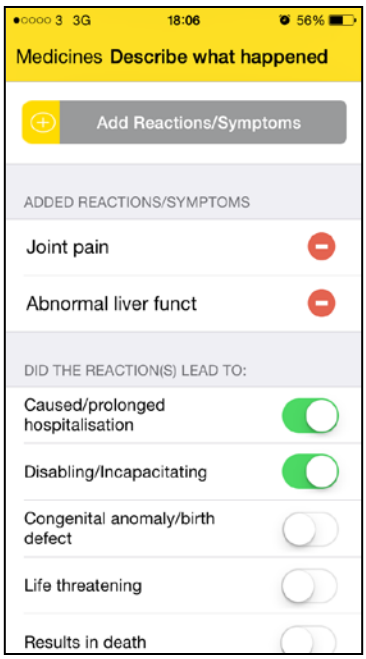
If you have any feedback on the app, either about how it works now, or features you would like to be added in future, please email us: web-radr@mhra.gsi.gov.uk

Downloaded the app on iOS or Android.









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3 **Pseudoephedrine and ephedrine: update on managing risk of misuse**

Implementation of measures to regulate sales, together with the additional voluntary actions overseen by the pharmacy profession, has made an important contribution to managing the risk of misuse of pseudoephedrine and ephedrine in the UK.

Pseudoephedrine and ephedrine are medicines used as nasal decongestants, which are available from pharmacies. Between 2007 and 2008, we introduced restrictions on their use because of concern that medicines containing these active substances could be used in the illicit manufacture of the Class A controlled drug methylamphetamine.

Sales restrictions
Since April 2008, after public consultation and following advice from the Commission on Human Medicines (CHM), the following sales restrictions have been in place to manage the risk of misuse of pseudoephedrine and ephedrine:

- It is illegal to sell or supply any product that contains more than 720 mg pseudoephedrine or 180 mg ephedrine without a prescription
- It is illegal to sell or supply a combination of products that between them add up to more than 720 mg pseudoephedrine or 180 mg ephedrine without a prescription
- It is illegal to sell or supply a product that contains pseudoephedrine and a product that contains ephedrine in one transaction

Furthermore, the Royal Pharmaceutical Society advises that the sale and supply of these products must be made by a pharmacist or suitably trained pharmacy staff under the supervision of a pharmacist

Continual monitoring
The CHM has continually reviewed these measures and their effect on containing the potential problem of misuse (see Drug Safety Update October 2012 and a Public Assessment Report October 2012).

Impact of restrictions: 2015 review
Between June 2013 and March 2015 there have been a few reports from pharmacies of suspicious behaviour, which have been addressed according to established procedures. There has been no evidence of methylamphetamine manufacture from medicines. The evidence suggests that the restrictions are continuing to help manage the risk of misuse. Further information is available in our report: Pseudoephedrine and ephedrine: managing the risk of medicines misuse – September 2015.

Implementation of measures to regulate sales, together with the additional voluntary actions overseen by the profession, has made an important contribution to managing the risk of misuse of pseudoephedrine and ephedrine. The recommendation is that existing levels of monitoring, education, and awareness measures by pharmacists should be maintained. The success of these measures depends on the pharmacy profession, which makes a substantial contribution to managing the risk of misuse of these products.

Further information
Pseudoephedrine and ephedrine: quick reference guide from the Royal Pharmaceutical Society

Article citation: Drug Safety Update volume 9 issue 2 September 2015: 3

4 **Letters sent to healthcare professionals in August 2015**

Last month, a letter was sent regarding InductOs (solvent and matrix for implantation) to inform of a potential shortage of product.

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