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

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Contents

The Medicines and Healthcare products Regulatory Agency (MHRA) is the government agency 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 inform you of a risk of osteonecrosis of the external auditory canal associated with denosumab used in the treatment of osteoporosis. Alongside the previously reported risk to the jaw with denosumab, there are now reports of osteonecrosis of the external ear canal (page 2). Be aware of the risk of osteonecrosis of the external auditory canal as well as the jaw with denosumab and advise patients to report any symptoms that indicate that the jaw or ear may be affected. Please continue to report any cases to us via the Yellow Card Scheme.

We also feature an article about systemic cardiovascular effects associated with brimonidine gel (Mirvaso) for rosacea. Bradycardia, hypotension, and dizziness have been associated with application of the gel (page 3). Warn patients not to apply brimonidine gel to irritated or damaged skin, including after laser therapy to the skin.

You can also read the outcome of our regular review of the impact of the strategy to minimise the risk of misuse of pseudoephedrine and ephedrine (page 4) and learn more about how you can help us to support the safety of e-cigarettes and e-liquids by reporting suspected side effects and safety concerns (page 5).

Finally, in addition to the usual list of letters sent to healthcare professionals (page 6), this month we feature a short list of some of the Medical Device Alerts issued by MHRA in May (page 7). Be aware of any safety issues that affect devices used by your patients or in your practice and find out whether any recommended actions apply to you.

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Denosumab (Prolia, Xgeva▼): reports of osteonecrosis of the external auditory canal

Denosumab is associated with a risk of osteonecrosis of the jaw. Osteonecrosis of the external auditory canal has also been reported with denosumab.

Advice for healthcare professionals:

- the possibility of osteonecrosis of the external auditory canal should be considered in patients receiving denosumab who present with ear symptoms including chronic ear infections or in those with suspected cholesteatoma
- possible risk factors include steroid use and chemotherapy, with or without local risk factors such as infection or trauma
- advise patients to report any ear pain, discharge from the ear, or an ear infection during denosumab treatment
- report cases of osteonecrosis of any bone suspected to be associated with denosumab or any other medicine on a Yellow Card

Reports of osteonecrosis of the external auditory canal

In December 2015, we published a Drug Safety Update article about very rare reports of osteonecrosis of the external auditory canal with bisphosphonates. Since then, this possible risk has been kept under close review with denosumab, given that both denosumab and bisphosphonates are known to be associated with osteonecrosis of the jaw.

Worldwide, 5 reports of osteonecrosis of the external auditory canal have now been received for patients treated with 60 mg denosumab for osteoporosis.

The underlying possible pathological mechanism is considered to be similar to that for denosumab-related osteonecrosis of the jaw. As observed with bisphosphonates, the number of cases of osteonecrosis of the external auditory canal in association with denosumab is low compared with those of osteonecrosis of the jaw.

The product information for all denosumab-containing products is being revised to include a warning on the risk of osteonecrosis of external auditory canal. As for bisphosphonates, the risk of osteonecrosis at sites other than the jaw and the external auditory canal continues to be kept under close review.

Background

Denosumab is a human monoclonal IgG2 antibody. Denosumab 60 mg solution for injection (Prolia) is indicated for the treatment of osteoporosis in postmenopausal women and in men at increased risk of fractures, and for the treatment of bone loss associated with hormone ablation in men with prostate cancer at increased risk of fractures.

Denosumab 120 mg solution for injection (Xgeva▼) is indicated for the prevention of skeletal-related events (pathological fracture, radiation to bone, spinal cord compression, or surgery to bone) in adults with bone metastases from solid tumours, and for the treatment of adults and skeletally mature adolescents with giant cell tumour of bone that is unresectable or where surgical resection is likely to result in severe morbidity.

Article citation: Drug Safety Update volume 10 issue 11, June 2017: 1.

Brimonidine gel (Mirvaso): risk of systemic cardiovascular effects; not to be applied to damaged skin

Systemic cardiovascular effects including bradycardia, hypotension, and dizziness have been reported after application. It is important to avoid application to irritated or damaged skin, including after laser therapy.

Advice for healthcare professionals:

- cases of bradycardia, hypotension (including orthostatic hypotension), and dizziness after application of brimonidine gel have been reported, some of which required hospitalisation
- some cases were associated with application of brimonidine gel after laser procedures to the skin, which possibly caused increased absorption of the gel
- warn patients not to apply brimonidine gel to irritated or damaged skin, including after laser therapy to the skin

Brimonidine (Mirvaso) is a topical gel indicated for the symptomatic treatment of facial erythema of rosacea in adults. It is an α-2 adrenergic agonist.

A routine European review identified post-marketing reports, including a small number of Yellow Cards, consistent with systemic (central) α-2 adrenergic effects, including bradycardia, hypotension (including orthostatic hypotension), and dizziness. Some patients required hospitalisation. Dizziness is reported to occur uncommonly, with an estimated frequency of less than 10 in 1,000 patients using brimonidine gel. Hypotension and bradycardia are reported to occur rarely, with an estimated frequency of less than 1 in 1,000 patients.

In approximately 30% of the cases most strongly suggestive of a cardiovascular effect, events occurred following application of brimonidine gel after laser therapy to the skin.

To minimise the possibility of systemic absorption, you should warn patients not to apply brimonidine gel to irritated or damaged skin, including after laser therapy to the skin.

Any suspected adverse reactions to brimonidine gel or any other medicines should be reported to us on a Yellow Card.

Article citation: Drug Safety Update volume 10 issue 11, June 2017: 2.

Pseudoephedrine and ephedrine: regular review of minimising risk of misuse in the UK

Sales restrictions introduced in 2008 continue to be successful in managing the risk of misuse of pseudoephedrine and ephedrine.

Background

Pseudoephedrine and ephedrine are available from pharmacies as nasal decongestants. Between 2007 and 2008, we introduced restrictions on their sale because of concerns 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.

Continued monitoring

CHM and MHRA have regularly reviewed these measures and the impact on containing the potential problem of misuse (see Drug Safety Update October 2012, September 2015, and Public Assessment Report October 2015).

Impact of restrictions: 2017 review

Between April 2015 and July 2016, pharmacies continued to be vigilant about suspicious behaviour in relation to sales of medicines containing pseudoephedrine. One case of suspicious behaviour has been reported. We have also received reports of two small-scale methylamphetamine labs using pseudoephedrine medicines. These reports are not considered to reflect a wider concern.

The evidence suggests that the restrictions are successfully continuing to manage the risk of misuse. Further information is available in the June 2017 Public Assessment Report.

The measures to regulate sales, together with additional vigilance by pharmacists, remain in force.

Further information

Pseudoephedrine and ephedrine: regular review of minimising the risk of misuse in the UK – MHRA UK Public Assessment Report – June 2017

Pseudoephedrine and ephedrine: Look, Listen and Report your suspicions; a quick reference guide

Article citation: Drug Safety Update volume 10 issue 11, June 2017: 3.

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e-cigarettes and refill containers (e-liquids): report suspected side effects and safety concerns

Use the Yellow Card Reporting Scheme to support the safety of e-cigarettes and refill containers (e-liquids).

What and how to report

Members of the public and healthcare professionals can use the Yellow Card Scheme website to report any suspected side effects or safety concerns with e-cigarettes and the e-liquids used for vaping.

These issues could include:

- suspected side-effects that occurred after the use of e-cigarettes and e-liquids
- harm to children or non-users, including accidental poisoning
- safety issues or defects with e-cigarette devices

Your information will aid us in identifying previously unrecognised side effects or issues, and thereby help to support the safety of e-cigarettes. MHRA is working with Trading Standards to ensure products on the UK market meet acceptable safety standards.

An infographic is available as a reminder to report any unexpected side effects to the Yellow Card Scheme.

Background

An e-cigarette (electronic cigarette) is a product that can be used to inhale nicotine-containing vapour via a mouth piece (also known as ‘vaping’). E-cigarettes can be disposable, have a refillable tank, or be rechargeable with single-use cartridges.

The Tobacco Products Directive has introduced new minimum standards for the safety and quality of e-cigarettes and their refill containers and a notification scheme for e-cigarettes and e-liquids containing less than 20 mg/mL nicotine with a volume 2 mL or under. It came fully into effect in the UK on 20 May 2017. The Directive also introduced new rules to ensure more information is made available to consumers with the product they buy and to protect children from starting to use e-cigarettes.

MHRA is responsible for the UK notification scheme for e-cigarettes and e-liquids. You can find information about the scheme and a list of notified products here.

About Yellow Card

Don't forget, as well as reports for e-cigarettes, the Yellow Card Scheme can be used to report adverse reactions for all medicines, including nicotine-containing products that are licensed as medicines, herbal medicines and homeopathic remedies, and all medical devices available on the UK market.

The Yellow Card Scheme is vital for MHRA to monitor the safety of medicines and healthcare products in the UK.

Article citation: Drug Safety Update volume 10 issue 11, June 2017: 4.

Letters sent to healthcare professionals in May 2017

In May 2017, letters were sent about:

- Pharmalgen (Bee Venom and Wasp Venom) Initial kits: implementation of serial dilution protocol for up-dosing; risk of dosing errors (see dilution chart)
- Bendamustine (Levact): increased mortality observed when used in non-approved combination treatments or outside approved indications
- ERWINASE: notice of special handling instructions—vials of ERWINASE from batch 182G should be used with a 5-micron filter needle

Article citation: Drug Safety Update volume 10 issue 11, June 2017: 5.

Medical Device Alerts issued in May 2017

In this monthly update, we will be highlighting selected Medical Device Alerts that have been issued recently by MHRA. Be aware of any device issues affecting your patients or your practice and find out whether any recommended actions apply to you. Please note, this is not an exhaustive list of medical device alerts. For all Medical Device Alerts from MHRA, see Alerts and recalls for drugs and medical devices.

In May 2017, Medical Device Alerts were issued by MHRA about:

- all LIFEPAK 1000 automatic external defibrillators (AEDs), manufactured by Physio-control: risk of device shutting down unexpectedly during patient treatment and possible failure to deliver therapy
- biological replacement pericardial aortic heart valves; Mitroflow LX (sizes 19mm and 21mm), manufactured by LivaNova: risk of early structural valve deterioration
- all Accu-Chek® Insight insulin pumps, manufactured by Roche: updated information for battery management

Article citation: Drug Safety Update volume 10 issue 11, June 2017: 6.