

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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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.



MHRA is accredited by NICE to provide Drug Safety Update. Further information can be found on the NICE Evidence Search portal: www.evidence.nhs.uk/

In our first article, read advice from a recent alert about higher than expected levels of histamine in some batches of gentamicin sulphate active pharmaceutical ingredient, used to manufacture gentamicin (page 2).

In our second article, we remind you about warnings for quinine regarding the potential for QT-interval-prolonging effects and highlight recent updates on interacting medicines, including some anticonvulsants (page 3).

In our third article, we remind you of advice to avoid inadvertent switching between oral tacrolimus products following the launch of new products, including generic formulations (page 4).

Next, we bring news of the second social media campaign to promote the reporting of suspected adverse drug reactions (ADRs) to the Yellow Card Scheme (page 5). This year the campaign focuses on over-the-counter medicines. Discuss with patients how reporting adverse drug reactions supports the safety of all medicines.

In our fifth article, we update advice about switching antiepileptic drugs following a review by the Commission on Human Medicines (page 7).

Finally, further to our 2016 advice, we highlight Public Health England's updated advice on live vaccination of infants born to a mother who received immunosuppressive biological therapy during pregnancy (page 9).

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Gentamicin: potential for histamine-related adverse drug reactions with some batches

Some batches of gentamicin sulphate active pharmaceutical ingredient (API) used to manufacture gentamicin may contain higher than expected levels of histamine, which is a residual from the manufacturing process. Monitor patients for signs of histamine-related adverse reactions.

Advice for healthcare professionals:

- monitor patients closely for potential adverse reactions associated with increased levels of histamine, including:
 - anaphylactoid reactions (for example, flushing, itching, urticaria, and shortness of breath)
 - hypotensive reactions
 - increased heart rate
- heart rate and blood pressure should be monitored throughout administration of gentamicin
- use caution when treating patients with gentamicin, especially if using at the same time as other drugs known to cause histamine release
- paediatric patients and patients with severe renal impairment may be more susceptible to the effects of exogenous histamine, therefore these patients should be monitored more closely
- report suspected adverse drug reactions to gentamicin on a [Yellow Card](#)

We have been informed that some batches of the gentamicin sulphate active pharmaceutical ingredient (API), which is used to manufacture the antibiotic gentamicin, may contain higher than expected histamine levels. Histamine is a residual from the manufacturing process. Batches potentially affected were produced with the API between the second half of 2014 and June 2017.

On 17 October 2017, a [Caution in Use alert](#) was issued via the Central Alerting System. We are working with the Marketing Authorisation Holders for these products to investigate the issue further. A recall is not considered appropriate at this stage. The following products are potentially affected:

Product	Marketing Authorisation Holder
Gentamicin 1 mg/mL Solution for Infusion	B Braun Melsungen AG
Gentamicin 3 mg/mL Solution for Infusion	B Braun Melsungen AG
Cidomycin (Gentamicin) 80 mg/2 mL Solution for Injection	Sanofi
Gentamicin 40 mg/mL Injection	Hospira UK Limited
Gentamicin Intrathecal 5 mg/mL Solution for Injection	Zentiva
Gentamicin Paediatric 20 mg/2 mL Solution for Injection	Zentiva
Gentamicin 40 mg/mL Solution for Injection	Amdipharm UK Limited
Gentamicin 10 mg/mL Solution for Injection or Infusion	Wockhardt UK Limited
Gentamicin 40 mg/mL Solution for Injection or Infusion	Wockhardt UK Limited

Any suspected adverse drug reactions with gentamicin should be reported to us at <https://yellowcard.mhra.gov.uk/>

Article citation: Drug Safety Update volume 11 issue 4; November 2017: 1.

Quinine: reminder of dose-dependent QT-prolonging effects; updated medicine interactions

Quinine has dose-dependent QT-interval-prolonging effects and should be used with caution in patients with risk factors for QT prolongation or in those with atrioventricular block.

Advice for healthcare professionals:

- be aware of dose-dependent effects on the QT interval and use caution if prescribing quinine in patients:
 - with conditions that predispose to QT prolongation such as pre-existing cardiac disease or electrolyte disturbance
 - taking other medicines that could prolong the QT interval
 - with atrioventricular block
- monitor patients closely if administration of quinine with phenobarbital or carbamazepine is necessary; serum levels of these anticonvulsant medicines could become raised and cause anticonvulsant toxicity
- consult the Summary of Product Characteristics for a full list of interacting medicines and potential adverse reactions
- report suspected adverse drug reactions with quinine on a [Yellow Card](#)

Cardiac effects

Quinine is well known to have effects on the QT interval. A [2017 routine EU review](#) recommended that warnings for dose-dependent QT-prolonging effects should be present in the product information for all quinine-containing medicines.

Use caution if prescribing quinine medicines in patients with conditions that predispose to QT prolongation, such as pre-existing cardiac disease or electrolyte disturbances, or in patients taking other medicines that prolong the QT interval (see [table from Stockley's Drug Interactions for examples](#)). Use caution when prescribing quinine to patients with atrioventricular block since quinine could aggravate conduction deficits.

CYP3A4-mediated interactions with other drugs

Quinine is metabolised via hepatic oxidative cytochrome P450 pathways, predominantly by CYP3A4. The 2017 review identified a pharmacokinetic study¹ reporting that serum levels of phenobarbital or carbamazepine could become raised when these anticonvulsant drugs are used concomitantly with quinine. Although data appear to be limited to this study, it is advisable to monitor for evidence of toxicity if quinine is used concomitantly.

Since CYP3A4 is involved in the metabolism of many other drugs, consult the section 4.5 of the Summary of Product Characteristics (SPC) for a list of interacting medicines before prescribing quinine.

1. Amabeoku GJ, et al. [Pharmacokinetic interaction of single doses of quinine and carbamazepine, phenobarbitone and phenytoin in healthy volunteers](#). *East Afr Med J* 1993; 70: 90-93.

Reminder of other important adverse reactions associated with quinine

Quinine has been used in the UK for the treatment of nocturnal leg cramps for many years; however, you should be aware of important events that can occur in patients taking this medicine. Consult the SPC for important recommendations about the proper use of quinine. Report suspected adverse drug reactions with quinine on a [Yellow Card](#).

Further information

[EMA. Scientific conclusions and grounds for the variation for quinine medicines.](#)

[Quinine: not to be used routinely for nocturnal leg cramps. Drug Safety Update, June 2010.](#)

[BNF. Quinine interactions.](#)

Article citation: Drug Safety Update volume 11, issue 4; November 2017: 2.

Oral tacrolimus products: reminder to prescribe and dispense by brand name only

Inadvertent switching between tacrolimus products has been associated with reports of toxicity and graft rejection. If you switch a patient to a different brand, ensure they receive careful supervision and therapeutic monitoring by an appropriate specialist.

Reminder of prescribing and dispensing advice

Tacrolimus is an immunosuppressant drug that may be given orally to prevent or treat organ transplant rejection. Tacrolimus has a narrow therapeutic index, and even minor differences in blood levels have the potential to cause graft rejection reactions or toxicity.

In June 2012, following reports of graft rejections and toxicity resulting from switching between products, we issued a Drug Safety Update recommending that all oral tacrolimus products should be prescribed and dispensed by brand name only. We are aware of new oral tacrolimus products on the market or about to be launched. [Recommendations from June 2012](#) remain in place, and also apply to any new tacrolimus products launched since this advice was issued. This includes generic products and prolonged-release formulations.

Further information

[Oral tacrolimus products: prescribe and dispense by brand name only. Drug Safety Update, June 2012.](#)

BNF. [Tacrolimus](#).

Article citation: Drug Safety Update volume 11, issue 4; November 2017: 3.

Support our second social media campaign for suspected adverse drug reactions

We are running a second social media campaign to promote the reporting of suspected adverse drug reactions (ADRs) to the Yellow Card Scheme in support of the ADR awareness week from 20 to 24 November 2017. The main message of the campaign is that reporting helps the safe use of medicines to protect public health. This year there is a focus on over-the-counter medicines; however, the message is applicable to those on general sale.

What can healthcare professionals and their organisations do?

- follow us on our social media channels and show your support for the importance of [reporting suspected adverse drug reactions](#) (ADRs) by retweeting, commenting, liking, and sharing material with your social media contacts. You can follow us via:
 - Twitter ([@MHRAGovuk](#) and [@MHRAMedicines](#))
 - [YouTube](#)
 - [Facebook](#)
 - [LinkedIn](#)
- encourage the dialogue between your colleagues and your patients about the importance of reporting suspected ADRs
- don't delay in reporting any suspected ADRs to the [Yellow Card Scheme](#) or via the Yellow Card app (download from the [Apple App Store](#) or [Google Play Store](#)).
- engage locally with your [regional Yellow Card Centre](#) or your local Medication Safety Officer (MSO) in England at your hospital trust

Over-the-counter medicines: why reporting adverse reactions is still important

Over-the-counter medicines are an important way for patients to manage their own health. Medicines available over-the-counter are acceptably safe and effective when used in accordance with instructions and under the guidance of pharmacists.

MHRA continually reviews the safety of all medicines, including those available over-the-counter or on general sale. Some adverse drug reactions can only be identified when medicines are used for a long time in a wide range of different people, so it is very important that adverse drug reactions are reported to the Yellow Card Scheme, even when the medicine was not prescribed. Healthcare professionals and patients can also report cases of medication error or misuse or abuse of medicines; helping to identify important safety issues.

You can raise awareness with your patients by talking about these key messages:

- just because you can buy a medicine without a prescription, it doesn't mean you might not have any suspected side effects
- always read the information, including the leaflet, about how much medicine to take, how to take it, and about any known side effects
- do not exceed the recommended dose or duration of treatment
- reporting suspected side effects to the Yellow Card Scheme helps to identify information about a medicine that might not have been known before
- patients should tell any healthcare professional about side effects they may have had and can report directly themselves via the [Yellow Card Scheme website](#)
- it's also useful to report suspected side effects that happen when taking more than one medicine, or after long-term use, or from interactions with food or other products

Campaign material freely available for reuse include a general [animation](#) about reporting and [infographics](#), which are also available on the [Yellow Card reporting website](#).



The reporting of suspected ADRs is key to patient safety. This campaign builds on the first award-winning EU wide campaign, led by the MHRA, which reached over 2.5 million people to help encourage greater local and national awareness about the importance of reporting to support the earlier detection of safety issues.

We also have dedicated [guidance on the Yellow Card Scheme for healthcare professionals](#) including accredited CPD [e-learning](#) modules.

Healthcare professionals are reminded to report any suspected adverse reactions to the [Yellow Card Scheme](#) to all medicines including:

- vaccines
- blood factors and immunoglobulins
- herbal medicines
- homeopathic remedies

Article citation: Drug Safety Update volume 11 issue 4; November 2017: 4.

Antiepileptic drugs: updated advice on switching between different manufacturers' products

In addition to the 3 risk-based categories of antiepileptic drugs, patient-related factors should be considered when deciding whether it is necessary to maintain continuity of supply for a specific product.

Advice for healthcare professionals:

- [core advice from 2013](#) remains in effect for prescribing antiepileptic drugs to manage epilepsy
- consult the 3 categories of antiepileptic drugs when deciding whether it is necessary to maintain continuity of supply of a specific manufacturer's product
- as well as the classification, when evaluating whether continuity of supply should be maintained for category 2 or 3 medicines, consider:
 - perception by patients of differences in supply, for example differences in product presentations
 - co-morbid autism, mental health issues, or learning disability
- if you think a patient should be maintained on a specific manufacturer's product, prescribe either by specifying brand name or by using the generic drug name and name of the manufacturer

CHM review and update

In November 2013, we issued advice about [switching between different manufacturers' products](#) of an oral antiepileptic drug. In September 2016, the [Commission of Human Medicines](#) (CHM) reviewed this advice following feedback and requests for clarification from patients and healthcare professionals. CHM maintained their previous advice that when considering switching, antiepileptic drug could be classified into 3 categories and that, although the reports of loss of seizure control and/or worsening of side effects occur around the time of switching between products could be explained as chance associations, the effect of switching could not be ruled out in all cases.

For drugs in Category 3, therapeutic equivalence between branded and generic products (and between different generics) can be assumed, but other factors are important when considering whether switching is appropriate. Differences between alternative products (for example, product name, packaging, appearance, and taste) may be perceived negatively by patients and/or carers, and may lead to dissatisfaction, anxiety, confusion, dosing errors, and reduced adherence. In addition, difficulties for patients with co-morbid autism, mental health problems, or learning disability should also be considered.

For drugs in Category 2 similar considerations apply. It may also be necessary to consider clinical factors such as seizure frequency, treatment history, and the potential implications for the individual of having a breakthrough seizure.

The table below summarises the different categories of antiepileptic drugs, and advice for prescribing.

	Drugs	More details on classification	Advice for prescribing
Category 1	Carbamazepine Phenobarbital Phenytoin Primidone	For these drugs, there are clear indications that clinically relevant differences between different manufacturers' products might occur, even when the pharmaceutical forms are the same and bioequivalence has been shown	Ensure that the patient is maintained on a specific manufacturer's product
Category 2	Clobazam Clonazepam Eslicarbazepine Lamotrigine Oxcarbazepine Perampanel Retigabine Rufinamide Topiramate Valproate Zonisamide	Drugs that do not fit into Category 1 or 3	Base the need for continued supply of a particular manufacturer's product on clinical judgement and consultation with patient and/or carer, taking into account factors such as seizure frequency and treatment history. Take into account patient/carer-related factors such as their negative perceptions about alternative products and/or other issues related to the patient should also be taken into account.
Category 3	Brivaracetam Ethosuximide Gabapentin Lacosamide Levetiracetam Pregabalin Tiagabine Vigabatrin	These drugs show all the following characteristics: <ul style="list-style-type: none"> • High solubility across the relevant range of pHs • Essentially complete absorption after oral administration • Dose-response curves for efficacy and safety are not steep • Therapeutic Index is not narrow 	For these drugs, the potential for clinically relevant differences to exist between different manufacturers' products is considered to be extremely low. However, consider other patient/carer-related factors, such as negative perceptions about alternative products and/or other issues related to the patient

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Updates to Public Health England's Green Book chapter on live attenuated vaccines

In an [April 2016 Drug Safety Update](#), we gave advice to avoid live attenuated vaccines in infants exposed to immunosuppressive treatment from the mother either in utero or via breastfeeding.

Public Health England has now updated [chapter 6 of the Green Book](#) to specify that children born of mothers who were on immunosuppressive biological therapy during pregnancy will not be eligible to receive rotavirus vaccine (and will need to defer BCG, if indicated, for 6 months). If there is any doubt as to whether an infant due to receive a live-attenuated vaccine may be immunosuppressed due to the mother's therapy, including exposure through breastfeeding, specialist advice should be sought.

Article citation: Drug Safety Update volume 11 issue 4; November 2017: 6.

Letters sent to healthcare professionals in October 2017

In October 2017, the following letters were sent to relevant healthcare professionals to inform them of updated safety information:

- [Solu-Medrone 40 mg. Injectable methylprednisolone products containing lactose: new contraindication in patients allergic to cow's milk proteins treated for allergic conditions](#)

Article citation: Drug Safety Update volume 11, issue 4; November 2017: 7

Medical Device Alert issued in October 2017

For all Medical Device Alerts from MHRA, see [Alerts and recalls for drugs and medical devices](#).

An alert was recently issued by MHRA about:

- [Professional use HIV test: Alere HIV Combo – risk of false positive results](#)

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