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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Our first article highlights regulatory action taken following 2 observational studies linking hydrochlorothiazide-containing medicines, particularly in long-term use, with an increased risk of non-melanoma skin cancer. See page 2 for measures to minimise risk, including that patients should be advised to limit exposure to, and use adequate protection against, sunlight and UV rays and to be vigilant for suspicious moles and skin lesions.

In our next article, we advise you to carefully assess the benefits and risks and consider other therapeutic options before prescribing systemic and inhaled fluoroquinolone antibiotics in patients at increased risk of aortic aneurysm and dissection (page 4).

On page 6, read interim results from the STRIDER clinical trial, which assessed sildenafil during pregnancy in off-label use for intrauterine growth restriction.

On page 8, we ask you to show your support for the EU-wide ADR awareness week campaign taking place from 19–23 November 2018, by sharing material on social media and discussing the importance of reporting side effects with your colleagues and with patients, parents, and caregivers. This year the key message is that reporting relevant suspected adverse drug reactions to the Yellow Card Scheme helps the safe use of medicines in babies, children, and pregnant and breastfeeding women.

On page 11 and 12, we highlight letters and alerts sent in October 2018, including a letter advising of the extension of use beyond the labelled expiry date for specific lots of Jext adrenaline auto-injectors during the current supply disruption.

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Hydrochlorothiazide: risk of non-melanoma skin cancer, particularly in long-term use

Advise patients taking hydrochlorothiazide-containing products of the cumulative, dose-dependent risk of non-melanoma skin cancer, particularly in long-term use, and the need to regularly check for (and report) any suspicious skin lesions or moles. Counsel patients to limit exposure to sunlight and UV rays and to use adequate sun protection.

Advice for healthcare professionals:

- pharmacoepidemiological studies have shown a dose-dependent increased risk of non-melanoma skin cancer (basal cell carcinoma [BCC] and squamous cell carcinoma [SCC], including SCC lip cancer) with exposure to increasing cumulative doses of hydrochlorothiazide (see table of data below)
- inform patients taking hydrochlorothiazide-containing products of the risk of non-melanoma skin cancer, particularly in long-term use, and advise them to regularly check for and report any new or changed skin lesions or moles
- reconsider the use of hydrochlorothiazide in patients who have had previous skin cancer
- examine all suspicious moles or skin lesions (potentially including histological examination of biopsies)
- advise patients to limit their exposure to sunlight and UV rays and use adequate protection when exposed to sunlight and UV rays to minimise the risk of skin cancer
- report suspected adverse reactions associated with medicines to the Yellow Card Scheme

Study data showing increase risk of skin cancer

Two recent pharmaco-epidemiological studies[1,2] in Danish nationwide data sources (including the Danish Cancer Registry and National Prescription Registry) have shown a cumulative, dose-dependent, association between hydrochlorothiazide and non-melanoma skin cancer. The known photosensitising actions of hydrochlorothiazide could act as possible mechanism for this risk. The table below summarises the main findings in these studies:

Type of cancer	Number of cases	Number of population controls	Adjusted odds ratios with ever-use of hydrochlorothiazide (95% CI)	Adjusted odds ratios with high* cumulative use of hydrochlorothiazide (95% CI)	Adjusted odds ratios with highest** cumulative use of hydrochlorothiazide (95% CI)
BCC	71, 533	1,430,833	1.08 (1.05–1.10)	1.29 (1.23–1.35)	1.54 (1.38–1.71)
SCC	8,629	172,462	1.75 (1.66–1.85)	3.98 (3.68–4.31)	7.38 (6.32–8.60)
Lip cancer	633	63,067	2.1 (1.7–2.6)	3.9 (3.0–4.9)	7.7 (5.7–10.5)

Table: Study findings
BCC=basal cell carcinoma. SCC= squamous cell carcinoma. CI=confidence interval. *High cumulative hydrochlorothiazide use for BCC and SCC[1] is ≥50,000 mg (corresponding to 12.5 mg hydrochlorothiazide taken daily for about 11 years), high cumulative hydrochlorothiazide use for SCC lip cancer[2] is ≥25,000 mg. ** Highest cumulative hydrochlorothiazide use for BCC and SCC is ≥200,000 mg, highest cumulative hydrochlorothiazide use for lip cancer is ≥100,000 mg.

1. Pedersen SA, et al. Hydrochlorothiazide use and risk of non-melanoma skin cancer: A nationwide case-control study from Denmark. *J Am Acad Dermatol* 2018; 78: 673–81.

2. Pottegård A, et al. Hydrochlorothiazide use is strongly associated with risk of lip cancer. *J Intern Med* 2017; 282: 322–31.

The study authors' analyses did not find a similar association for risk of BCC or SCC[1] and SCC lip cancer[2] with overall or cumulative use of other diuretics and other hypertensives, including bendroflumethiazide, calcium channel blockers, angiotensin-converting enzyme inhibitors, angiotensin II receptor antagonists, and furosemide.

Pedersen and colleagues reported that, assuming causality, 9 in 100 SCC cases and fewer than 1 in 100 BCC cases diagnosed during the study period may have been attributed to hydrochlorothiazide use.[1] Pottegård and colleagues reported that 11 in 100 of SCC lip cancer cases occurring in the study period may have been attributed to hydrochlorothiazide use.

About non-melanoma skin cancer

Non-melanoma skin cancer is a rare event. Incidence rates highly depend on skin phenotypes and other factors, which leads to different baseline risks and varying incidence rates in different countries. Estimated incidence rates in Europe range from 1–34 cases per 100,000 people per year for SCC and 30–150 per 100,000 people per year for BCC.

In the UK, rates of SCC and BCC vary by region. One systematic review estimated average incidence rates in England of 23 cases of SCC per 100,000 person-years and 76 cases of BCC per 100,000 person-years.[3] Average rates in Scotland were 27 cases of SCC per 100,000 person-years and 90 cases of BCC per 100,000 person-years, with similar incidence also reported for Northern Ireland (31 cases and 87 cases per 100,000 person-years, respectively).[3]

3. Lomas A, et al. A systematic review of worldwide incidence of nonmelanoma skin cancer. *Br J Dermatol* 2012; **166:** 1069–80.

Based on the results of the two Danish epidemiological studies, a best estimate of the increased risk is 7.7-fold for SCC and 1.5-fold for BCC based on a length of usage of hydrochlorothiazide 12.5mg daily for 44 years or 25 mg daily for 22 years. For hypertension, products containing 25 mg of hydrochlorothiazide are indicated only if patients are not adequately controlled on lower-dose products.

The Summary of Product Characteristics and Patient Information Leaflets for all the concerned products have been updated to inform of the risk of non-melanoma skin cancer. A letter about the risk and advice has also been sent to prescribers and dispensers of hydrochlorothiazide-containing medicinal products.

Background

Hydrochlorothiazide-containing medicinal products are used to treat hypertension, as well as oedema associated with cardiac or hepatic disease and chronic heart insufficiency (heart failure). In the UK, hydrochlorothiazide is only available in fixed-dose combination with other medicines. We estimate that approximately 28,000 patients in the UK take medicines containing hydrochlorothiazide.†

Report suspected adverse drug reactions on a Yellow Card

Please continue to report suspected adverse drug reactions associated with hydrochlorothiazide to MHRA through the Yellow Card Scheme.

Article citation: Drug Safety Update volume 12, issue 4: November 2018: 1.

† Data has been extrapolated to the UK population from the Clinical Practice Research Datalink (CPRD), which is a representative sample of approximately 750 primary care practices across the UK. The data are based on prescriptions issued to patients and therefore it is not possible to confirm whether the medicine was dispensed and subsequently consumed by the patient. It also does not include medicines prescribed in hospital settings. The CPRD data are obtained under licence from the UK MHRA, however the interpretation and conclusions from this data are that of the authors alone.

Systemic and inhaled fluoroquinolones: small increased risk of aortic aneurysm and dissection; advice for prescribing in high-risk patients

In patients at risk for aortic aneurysm and dissection, fluoroquinolones should only be used after careful assessment of the benefits and risks and after consideration of other therapeutic options.

Advice for healthcare professionals:

- systemic (by mouth or injection) and inhaled fluoroquinolones may be associated with a small increased risk of aortic aneurysm and dissection, particularly in older patients
- fluoroquinolones should only be used after careful benefit-risk assessment and after consideration of other therapeutic options in patients at risk for aortic aneurysm and dissection
- Conditions predisposing to aortic aneurysm and dissection include:
  - a family history of aneurysm disease
  - diagnosis with pre-existing aortic aneurysm and/or aortic dissection
  - other risk factors or conditions predisposing for aortic aneurysm and dissection (for example, Marfan syndrome, vascular Ehlers-Danlos syndrome, Takayasu arteritis, giant cell arteritis, Behcet's disease, hypertension, and known atherosclerosis)
- advise patients, particularly elderly people and those at risk, about rare events of aortic aneurysm and dissection and of the importance of seeking immediate medical attention in case of sudden-onset severe abdominal, chest or back pain
- report suspected adverse drug reactions to fluoroquinolone antibiotics on the Yellow Card website or via the Yellow Card app (download it from the Apple App Store, or Google Play Store

Data suggesting increased risk of aortic aneurysm and dissection

Fluoroquinolones are antibiotics authorised for serious, life-threatening bacterial infections (see list of fluoroquinolone antibiotics below).

Data from epidemiologic and non-clinical studies indicate an increased risk of aortic aneurysm and dissection after intake of fluoroquinolones.

Epidemiological studies suggest an increased risk of aortic aneurysm and dissection with fluoroquinolone usage, particularly in older patients. One study[1] reported a rate of aortic aneurysm or dissection of 1.2 cases per 1000 person-years among fluoroquinolone treatment episodes versus 0.7 cases per 1000 person-years among amoxicillin treatment episodes, corresponding to an estimated absolute difference of 82 (95% confidence interval 15–181) cases of aortic aneurysm or dissection by 60 days per 1 million treatment episodes. Another study[2] of patients aged 65 years and older in Canada reported a rate of aortic aneurysms diagnosed in hospital and emergency departments as 3.5 per 1000 person-years for patients currently using fluoroquinolones versus 1.3 per 1000 person-years for patients not using fluoroquinolones.

In the studies, the increased risk for aortic aneurysm was seen within the first 1–2 months of treatment with systemic fluoroquinolones.[1,2] The data do not allow for differentiation between risk for different fluoroquinolones or durations of treatment.

These findings indicate that systemic or inhaled fluoroquinolones might contribute to aortic aneurysm and dissection, in particular in patients with pre-existing risk factors.

1. Pasternak B, et al. Fluoroquinolone use and risk of aortic aneurysm and dissection: nationwide cohort study. *BMJ* 2018; 360: k678.

2. Daneman N, et al. Fluoroquinolones and collagen associated severe adverse events: a longitudinal cohort study. *BMJ Open* 2015; 5: e010077.

About aortic aneurysm and dissection

Aortic aneurysm and dissection are rare events, occurring in about 3–30 of 100,000 persons per year in the general population. Risk of aortic aneurism is increased in the presence of risk factors such as family history of aneurysm disease; pre-existing aortic aneurysm and/or aortic dissection; Marfan syndrome, vascular Ehlers-Danlos syndrome, Takayasu arteritis, giant cell arteritis, Behcet's disease, or hypertension; or known atherosclerosis.

While most abdominal aortic aneurysms are asymptomatic, some people describe persistent stomach, chest and/or lower back pain. Aortic dissection is usually accompanied by sudden, severe abdominal, chest, or back pain.

If initiating a course of a fluoroquinolone antibiotic, advise patients, particularly elderly people and those at risk, of the need to seek immediate medical attention if they develop sudden, severe pain in the abdomen, chest, or lower back since this may suggest a life-threatening aortic dissection (see letter to healthcare professionals).

Fluoroquinolone medicines available in UK

- Ciprofloxacin
- Levofloxacin
- Moxifloxacin
- Ofloxacin

Recommendations on restrictions on use

In October 2018 EMA's Pharmacovigilance Risk Assessment Committee (PRAC) recommended restricting the use of fluoroquinolone and quinolone antibiotics (by mouth, injection or inhalation) following a review of disabling and potentially long-lasting side effects reported with these medicines. The recommendation is now subject to further EU consideration and will take effect once a European Commission decision is issued. We will communicate the necessary actions to UK healthcare professionals following this Commission decision, which is expected in early 2019.

Report suspected adverse drug reactions via the Yellow Card scheme

Please continue to report any suspected adverse drug reactions via the Yellow Card Scheme. Remember only a suspicion is needed to report – if in doubt, please complete a Yellow Card.

Healthcare professionals, patients, and caregivers can report suspected side effects via the Yellow Card website or via the Yellow Card app. Download the app today via iTunes Yellow Card for iOS devices or via PlayStore Yellow Card for Android devices.

You can also use the app to access the latest safety information from the MHRA about medicines and medical devices on the Newsfeed. Search for medicines to see details of Yellow Card reports others have made. Medicines of interest can also be added to a Watch List to receive news and alerts about new side effects and safety advice as it emerges.

Article citation: Drug Safety Update volume 12, issue 4: November 2018: 2.

Sildenafil (Revatio and Viagra): reports of persistent pulmonary hypertension of the newborn (PPHN) following in-utero exposure in a clinical trial on intrauterine growth restriction

Sildenafil is not authorised for use in pregnancy for the treatment of intrauterine growth restriction. The STRIDER clinical trial, which was studying the use of sildenafil in pregnancy for intrauterine growth restriction, has been prematurely discontinued due to a higher incidence of persistent pulmonary hypertension of the newborn (PPHN) and neonatal mortality in the sildenafil arm of the study.

Advice for healthcare professionals:

- data from an independent clinical trial has shown potential harm, including increased risk of persistent pulmonary hypertension of the newborn (PPHN) and increased mortality, when used in pregnancy for early-onset intrauterine growth restriction (IUGR)
- sildenafil (Revatio and Viagra) is not authorised for the treatment of IUGR (see indication below)
- Revatio for the treatment of pulmonary arterial hypertension (PAH) is not recommended in pregnancy unless strictly necessary; Viagra is not authorised for use in women
- report suspected adverse drug reactions to sildenafil on a Yellow Card

Data from Dutch STRIDER study

Interim data from an independent clinical trial, the Dutch STRIDER (Sildenafil TheRapy in Dismal prognosis Early-onset fetal growth Restriction) study, suggest an increased risk of persistent pulmonary hypertension of the newborn (PPHN) and neonatal mortality when sildenafil was used in pregnancy for intrauterine (fetal) growth restriction compared with placebo. The group assigned to sildenafil had an incidence of 17 cases of PPHN in 64 babies (27%), including 11 deaths before discharge. In the placebo group, 3 of 58 babies (5%) had PPHN, with no reported deaths before discharge. These findings occurred in the absence of any benefit shown on the primary endpoint of neonatal survival until term age.

The Dutch STRIDER study was one of 5 independent studies by an international collaboration investigating the use of sildenafil for this unauthorised use. The 5 trials in the STRIDER Consortium were undertaken in the UK, Ireland, The Netherlands, New Zealand/Australia, and Canada. Pregnant women were randomised to generic sildenafil or placebo. Sildenafil was given in a dose of 25 mg three times a day to pregnant women for the treatment of severe intrauterine (fetal) growth restriction.

Details of the interim analysis of the Dutch STRIDER study are not yet available and the analysis by the STRIDER consortium of studies is awaited. A letter has been sent to relevant healthcare professionals to inform them of this information and that sildenafil should not be used in intrauterine (fetal) growth restriction.

UK arm of STRIDER study

The UK arm of the STRIDER trial, with a sample size of 135 women and a primary outcome of prolongation of pregnancy by 1 week, has completed and the results have been published.[1] The results of the UK STRIDER showed no difference in the median randomisation to delivery interval between women assigned to sildenafil (17 days [IQR 7–24]) and women assigned to placebo (18 days [IQR 8–28]; p=0·23).

1. Sharp A, et al. Maternal sildenafil for severe fetal growth restriction (STRIDER): a multicentre, randomised, placebo-controlled, double-blind trial. *Lancet Child Adolesc Health* 2018; 2: 93–102.

In the UK STRIDER trial, although not significant, higher percentages of neonatal death, neonatal morbidity, oxygen dependency, and surfactant use were observed among the sildenafil group compared to placebo.[1] No benefit in terms of longer interval until delivery was observed in the UK STRIDER. Although no significant difference in PPHN or neonatal mortality was identified in this arm of the trial, the smaller sample size has implications for the power of this study to identify an increase in these outcomes. The effects of the sildenafil in this unauthorised indication require further review of the full datasets from the STRIDER Studies, once these become available.

At this point, the benefit-risk balance of Sildenafil in the authorised indication of pulmonary artery hypertension remains unchanged for women who are pregnant (see below); however, this will be kept under review as further data emerge.

Background

Sildenafil is the active substance of the medicinal products Revatio and Viagra.

Revatio, and associated generic products, is authorised for the treatment of adults and children aged 1 to 17 years with pulmonary arterial hypertension (PAH). The product information for Revatio states that due to lack of data, Revatio should not be used in pregnant women unless strictly necessary. Viagra, and associated generic products, are used in the treatment of men with erectile dysfunction. It is not indicated for use in women.

Report suspected adverse drug reactions in pregnancy

Report to the Yellow Card Scheme any suspected adverse reactions associated with medicines taken during pregnancy experienced by women or the baby or child. Your report is essential to improve our understanding of medicines effects during pregnancy and ensure that healthcare professionals have up-to-date information on risks.

You can report on the Yellow Card website, through some clinical IT systems, or the free Yellow Card app. Download the app today via iTunes Yellow Card for iOS devices or via PlayStore Yellow Card for Android devices.

MHRA may request more detailed information and follow-up about the outcomes of the pregnancy as necessary. Therefore, when reporting, please provide sufficient contact information to allow for this. For more information, see Drug Safety Update, July 2018.

Article citation: Drug Safety Update volume 12, issue 4: November 2018: 3.

Support Yellow Card: improve the safety of medicines in pregnancy and breastfeeding, and in babies and children

Reporting suspected adverse drug reactions to the Yellow Card Scheme helps to support the safe use of medicines in babies, children, and pregnant and breastfeeding women. Show your support for this year's EU-wide ADR awareness week campaign from 19–23 November 2018, by sharing material on social media and discussing the importance of reporting suspected side effects with colleagues and parents and caregivers.

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 dialogue between your colleagues and patients, parents, and caregivers about the importance of reporting suspected ADRs, particularly those that occur during pregnancy and breastfeeding or in infants and children
- 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

Reporting improves medicines safety

The MHRA continually reviews the safety of all medicines. 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 suspected adverse drug reactions are reported to the Yellow Card Scheme.

Every report made by a healthcare professional or a patient or caregiver plays a critical role in understanding the benefits and risks of medicines in clinical use, allowing action to be taken to minimise risks. Reporting helps to improve the safety of medicines for all patients and, in some cases, can result in better tailored prescribing advice, which can help improve adherence to treatment.

Medicines in pregnancy and breastfeeding

Medicines should not typically be taken in pregnancy and during breastfeeding. However, some women will need to take medicines to protect their health and that of the baby.

When a medicine is licensed, there is often limited information on effects from use in pregnancy and breastfeeding. Therefore, information about any suspected adverse drug reactions in the mother or child is essential to improve understanding of a medicine's effects and to ensure that healthcare professionals have the best available information on risks. For more about what key elements to include when reporting a suspected adverse drug reaction during pregnancy or breastfeeding, see article in Drug Safety Update, July 2018.

Risks in infants and children exposed to medicines during pregnancy have been identified with the help of healthcare professionals reporting to spontaneous reporting schemes like Yellow Card and to registries. One example of this is mycophenolate mofetil and risk of serious birth defects and spontaneous abortion.

Encourage women who are pregnant or breastfeeding, or who are planning a pregnancy, to talk to their healthcare professional about medicines they are taking. This includes any over-the-counter or herbal or complementary medicines.

It is very important that women who are pregnant do not stop taking prescribed medicines without talking to their doctor. Stopping some medicines suddenly can cause harm to mother and baby.

If a woman needs to take a medicine during pregnancy or breastfeeding, make sure they are fully aware of the benefits and risks of medicines they are taking, are provided with a patient information leaflet, and that they know how to report suspected side effects.

Medicines in babies and children

There has been an increase in the number of medicines licensed for use in children, including more complex medicines, as a result of EU legislation. Many medicines are also used off-label in children without evidence to support efficacy and safety, although there are many instances where there is sufficient clinical knowledge for such medicines to be used safely. Children can also react to medicines very differently from adults. Despite these factors, there is under-reporting of suspected ADRs in children.[1,2,3]

All healthcare professionals involved in the care of paediatric patients should not only report suspected ADRs including those associated with off-label use, but also encourage parents and caregivers to report suspected ADRs in their child – they know their child best and can raise concerns about medicines that might not be otherwise identified. The MHRA systems handle any duplicate reports so this need not be a deterrent. All Yellow Card reports are confidential.

Medicines for Children is a partnership that produces information for parents and caregivers about medicines their child may be using. A leaflet from this organisation is available to assist discussion with parents and caregivers about side effects in children and the importance of reporting to the Yellow Card Scheme.

All Yellow Card reports related to suspected medicines-related harms in children are analysed alongside other safety information to assess medicines safety. Safety issues in children that were identified, in part, from reporting of adverse drug reactions include:

- Head lice eradication products: risk of serious burns if treated hair is exposed to open flames or other sources of ignition, eg, cigarettes
- Codeine for analgesia: restricted use in children because of reports of morphine toxicity

About the Yellow Card Scheme

All healthcare professionals, parents, and caregivers can report any suspected adverse reactions to the Yellow Card Scheme to medicines including:

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

1. Hawcutt DB, et al. Spontaneous adverse drug reaction reports for neonates and infants in the UK 2001-2010: content and utility analysis. *Br J Clin Pharmacol* 2016; **82:** 1601–12.

2. Heeley E, et al. Prescription-event monitoring and reporting of adverse drug reactions. *Lancet* **358:** 1872–73.

3. Thiesen S, et al. Incidence, characteristics and risk factors of adverse drug reactions in hospitalized children – a prospective observational cohort study of 6,601 admissions. *BMC Med* 2013; **11**: 237.

It is easy to report on the Yellow Card website or via the Yellow Card app. Download the app today via iTunes Yellow Card for iOS devices or via PlayStore Yellow Card for Android devices.

You can also use the app to access the latest safety information from the MHRA about medicines and medical devices on the Newsfeed. Search for medicines to see details of Yellow Card reports others have made. Medicines of interest can also be added to a Watch List to receive news and alerts about new side effects and safety advice as it emerges.

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

About the EU-wide ADR campaign

Campaign material freely available for reuse includes a general animation about reporting and infographics, which are also available on the Yellow Card reporting website.

The reporting of suspected ADRs is the key to patient safety. This year's campaign builds on the first and second award-winning EU wide campaigns, to help encourage greater local and national awareness about the importance of reporting to support the earlier detection of safety issues.

Article citation: Drug Safety Update volume 12, issue 4: November 2018: 4.

Letters and drug alerts sent to healthcare professionals in October 2018

Adrenaline autoinjector supply disruption

In response to the ongoing supply disruption of adrenaline autoinjectors, MHRA has allowed an extension of the use of specific lot (batch) numbers of Jext 150 mcg and Jext 300 mcg auto-injectors beyond the labelled expiry date by 4 months. See letter to healthcare professionals and Jext website for list of affected batches.

Advise patients to continue to check periodically the viewing window in the label of their autoinjector to ensure that the liquid inside is clear and colourless and replace if the liquid is discoloured.

See also the updated Department of Health and Social Care supply disruption alert (issued 15 October 2018) and NHS England Pharmacy and Dispensing Practice Q&A for adrenaline autoinjectors (updated 5 November 2018).

Please note during this period of reduced supply, expert clinical guidance is to use 25 kg as the cut-off for switching from 150 mcg to 300 mcg dosage for all devices. For two of the devices (Jext and Emerade), this will be an off-label change.

Epanutin (phenytoin) 30mg/5ml oral suspension supply disruption

All healthcare professionals who prescribe, dispense or administer Epanutin oral suspension should be aware of the recommendations of the Department of Health and Social Care Supply Disruption Alert for Epanutin (phenytoin) 30mg/5ml oral suspension. Different formulations of phenytoin are not interchangeable and careful management of switching and monitoring is required.

MHRA has approved the import of stock phenytoin oral suspension from Canada. This stock is considered an unlicensed preparation in the UK. See alert for important advice for prescribers and pharmacists.

Letters

In October 2018, the following other letters were sent to healthcare professionals:

- Rivaroxaban (Xarelto▼): increase in all-cause mortality, thromboembolic and bleeding events in patients after transcatheter aortic valve replacement in a prematurely stopped clinical trial
- Ozurdex 700 micrograms intravitreal implant (dexamethasone): silicone particle observed on implant during inspection
- Sildenafil (Revatio and Viagra) should not be used to treat intrauterine growth restriction
- Hydrochlorothiazide: Risk of non-melanoma skin cancer (basal cell carcinoma, squamous cell carcinoma)
- Epilim Chronosphere▼ (sodium valproate) 250mg Modified Release Granules – Temporary shortage in supply until 30 November 2018

Drug alerts and recalls

In October 2018, MHRA issued the following Alerts and recalls for drugs:

- Class 2 Medicines Recall: Ozurdex 700 micrograms intravitreal implant in applicator manufactured by Allergan Pharmaceuticals Ireland (MDR 95-08/18). Issued 5 October 2018. Allergan Pharmaceuticals Ireland is recalling specific batches due to the possibility that a single loose silicone particle of approximately 300microns in diameter may become detached.

Article citation: Drug Safety Update volume 12, issue 4: November 2018: 5.

Medical Device Alerts issued in October 2018

In this monthly update, we highlight selected Medical Device Alerts that have been issued recently by MHRA. 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.

The following alert was recently issued:

- CoaguChek Test Strips for Point of Care and Home Use – risk of false high results (MDA/2018/033). Issued 8 October 2018. Manufactured by Roche Diagnostics GmbH: affected CoaguChek test strips may give false high results for INR values above 4.5 when compared to laboratory results, this may lead to incorrect treatment decisions

You should also be aware of the recent recall of Clear and Simple Digital Pregnancy Tests (lot DM10220170710E) due to a small number of false positive results, see Field Safety Notice and MHRA press release for more information.

Article citation: Drug Safety Update volume 12, issue 4: November 2018: 6.