



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.



NICE has accredited the process used by the MHRA to produce Drug Safety Update guidance. More information on accreditation can be viewed on the [NICE website](https://www.nice.org.uk/accreditation).

To subscribe to monthly email alerts of Drug Safety Update see: <https://www.gov.uk/drug-safety-update>

First, on page 2, we advise of risk minimisation materials to support the safe use of paediatric formulations of direct-acting oral anticoagulants (DOACs) and ask healthcare professionals to ensure parents and caregivers are aware of these materials. We also provide further clarity on dose adjustment of DOAC medicines stratified by renal function.

On page 6, we remind healthcare professionals that accidental use of glucose-containing solutions as flush fluid for arterial lines may contaminate blood samples and result in falsely high glucose readings; this may lead to inappropriate insulin administration and subsequent hypoglycaemia.

Finally, we update previous advice regarding febuxostat, used for gout, and caution use in patients with a history of major cardiovascular disease. See page 8 for more information.

On page 12, we inform of recent National Patient Safety Alerts to remove from service Philips Health Systems V60 and V60 Plus ventilators and to recall from patients Emerade adrenaline auto-injectors. We also provide a summary of recent letters and notifications sent to healthcare professionals about medicines and medical devices. If you have been forwarded this issue of Drug Safety Update, subscribe directly [via our website](#).

Direct-acting oral anticoagulants (DOACs): paediatric formulations; reminder of dose adjustments in patients with renal impairment

Risk minimisation materials are available to support the safe use of new paediatric formulations of rivaroxaban (Xarelto) and dabigatran etexilate (Pradaxa). In addition, we ask healthcare professionals to consult the current advice to ensure that all patients with renal impairment receive an appropriate dose of DOAC medicines.

Advice for healthcare professionals:

- for paediatric use of these medicines, counsel parents and caregivers about the reconstitution and dosing of dabigatran granules and rivaroxaban granules to reduce the risk of medication errors; highlight the new instructions for use and other educational materials to support safe use in children
- ensure all patients with renal impairment receive an appropriate DOAC dose and monitor renal function during treatment to ensure dose remains appropriate
- report suspected adverse drug reactions associated with DOACs on a [Yellow Card](#), including thromboembolic or haemorrhagic events

Advice for healthcare professionals to give to patients and carers:

- DOACs are a group of medicines that help to prevent blood clots from forming – they are used to prevent strokes, heart attacks and other issues associated with blood clots
- parents and caregivers of children and adolescents prescribed these medicines should read and follow the Instructions for Use (IFU) booklet provided for instructions on how to prepare and administer these medicines
- all patients with renal impairment who are taking DOACs will be reviewed regularly to make sure they are taking the correct dose
- if patients or carers have any concerns about these medicines, they should talk to their healthcare professional

Availability of paediatric-specific formulations

Direct-acting oral anticoagulants (DOACs) are approved for a variety of uses related to anticoagulation (see full indications in further information section on page 5). Available DOACs include the direct factor Xa inhibitors apixaban (Eliquis), edoxaban (Lixiana), and rivaroxaban (Xarelto), and the direct thrombin inhibitor dabigatran etexilate (Pradaxa). Risk minimisation materials in the form of a prescriber guide and a patient alert card are in place for all DOACs.

Rivaroxaban and dabigatran are indicated for treatment of venous thromboembolism (VTE) and prevention of VTE recurrence in patients younger than 18 years.

For rivaroxaban, granules for oral suspension are available for children weighing up to 30kg. For dabigatran, a paediatric-specific formulation is available in Northern Ireland.

All parents and caregivers of children and adolescents prescribed these medicines should be advised to read and follow the Instructions for Use (IFU) provided in the carton ([rivaroxaban](#) and [dabigatran](#) in Northern Ireland). This shows how to prepare and take these formulations. In addition, an educational video showing how to prepare and administer rivaroxaban can be accessed via the patient alert card for rivaroxaban granules for oral suspension (video [online](#)).

Dosing and restrictions to the use of DOACs by renal function

Advice relating to paediatrics

Dosing of DOACs for children is based on body weight. For use of rivaroxaban in children aged younger than 1 year, renal function should be determined using serum creatinine. Rivaroxaban is not recommended in children younger than 1 year with serum creatinine results above 97.5th percentile (refer to the product information).

For all other children, the glomerular filtration rate should be determined (see BNF for Children resources on [Prescribing in renal impairment](#)). In paediatric patients with a glomerular filtration rate lower than 50mL/min/1.73m² treatment with rivaroxaban is not recommended (1 year and older) and use of dabigatran is contraindicated.

Advice relating to adults

Exposure to DOACs is increased in patients with renal impairment and it is therefore important that patients receive an appropriate dose adjusted for renal function.

Renal function in adults should be assessed by calculating creatinine clearance (CrCl) using the Cockcroft-Gault formula. See BNF resources on [Prescribing in renal impairment](#).

Patients with renal impairment should be reviewed regularly to ensure ongoing efficacy and safety, with dosing adjusted as required.

Recommendations for use of DOACs in patients with renal impairment were published in the [June 2020 issue of Drug Safety Update](#). Following queries from healthcare professionals, an updated table for adults is included below, which provides further clarity on dose adjustment in various indications and in patients with different severities of renal impairment.

Table 1 - Recommendations for DOACs in adults with renal impairment

Severity of renal impairment (creatinine clearance (CrCl))	Dabigatran	Apixaban	Edoxaban	Rivaroxaban
End stage (CrCl less than 15 mL per minute)	Contraindicated	Not recommended	Not recommended	Not recommended
Severe (CrCl 15 to 29 mL per minute)**	Contraindicated	To be used with caution in VTEp and VTEt; dose reduction is recommended in SPAF	Dose reduction recommended in all indications	Use with caution in all indications Dose adjustment is recommended in SPAF and should be considered in VTEt
Moderate (CrCl 30 to 49 mL per minute)**	Dose adjustment recommended in VTEp and should be considered in SPAF and VTEt	Dose reduction is required in SPAF in some patients*	Dose reduction recommended in all indications	Dose adjustment recommended in SPAF and should be considered in VTEt
Mild (CrCl 50 to 80 mL per minute)**	No dose adjustment required	Dose reduction is required in SPAF in some patients*	No dose adjustment required***	No dose adjustment required

CrCl = creatinine clearance. SPAF = prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation (NVAF). VTEp = prevention of VTE (venous thromboembolism) in elective hip or knee replacement surgery. VTEt = treatment of deep vein thrombosis and pulmonary embolism, and prevention of recurrent VTE events.

*In patients with serum creatinine ≥ 1.5 mg/dL (133 micromole/L) associated with age 80 years or older or body weight 60kg or lower. **For edoxaban moderate to severe renal impairment is defined as CrCl 15 to 50 mL/min. ***For patients with non-valvular atrial fibrillation (NVAF) and high creatinine clearance, in clinical trials there was a trend towards decreasing efficacy with increasing creatinine clearance observed for edoxaban versus well-managed warfarin, therefore edoxaban should be used in patients with NVAF and high CrCl only after a careful evaluation of the individual thromboembolic and bleeding risk.

Further information about DOACs

DOACs are oral anticoagulants. DOACs are indicated for:

- prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation with one or more risk factors, such as congestive heart failure, hypertension, age of 75 years and older, diabetes mellitus, prior stroke or transient ischaemic attack (all DOACs)
- treatment of deep vein thrombosis and pulmonary embolism, and prevention of recurrent events in adults (all DOACs)
- prevention of venous thromboembolism in adult patients undergoing elective hip or knee replacement surgery (dabigatran, apixaban and rivaroxaban)
- treatment of venous thromboembolic events (VTE) and prevention of recurrent VTE in paediatric patients from birth to less than 18 years of age (dabigatran and rivaroxaban)
- prevention of atherothrombotic events in adult patients after an acute coronary syndrome with elevated cardiac biomarkers when co-administered with acetylsalicylic acid (ASA) alone or with ASA plus clopidogrel or ticlopidine (2.5mg rivaroxaban only)
- prevention of atherothrombotic events in adult patients with coronary artery disease or symptomatic peripheral artery disease at high risk of ischaemic events when co-administered with ASA (2.5mg rivaroxaban only)

DOACs are [not recommended in patients with antiphospholipid syndrome](#). Dabigatran is contraindicated and other DOACs are not recommended in patients with prosthetic heart valves.

Report adverse drug reactions on a Yellow Card

Please continue to report suspected adverse drug reactions to the [Yellow Card scheme](#).

Healthcare professionals, patients, and caregivers are asked to submit reports using the Yellow Card scheme electronically using:

- the [Yellow Card website](#)
- the Yellow Card app; download from the [Apple App Store](#) or [Google Play Store](#)
- some clinical IT systems for healthcare professionals (EMIS, SystmOne, Vision, MiDatabank, and Ulysses)

When reporting please provide as much information as possible, including information about batch numbers, medical history, any concomitant medication, onset timing, treatment dates, and product brand name.

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Glucose solutions: recommendations to minimise the risks associated with the accidental use of glucose solutions instead of saline solutions in arterial lines

We remind healthcare professionals that accidental use of glucose-containing solutions as flush fluid for arterial lines may contaminate blood samples and result in falsely high glucose readings. This may lead to inappropriate insulin administration and subsequent hypoglycaemia. Healthcare professionals should use saline solutions to flush arterial lines and use pressure infusion bags with clear panels to ensure that the fluid label is visible at all times.

Advice for healthcare professionals:

- do not use glucose-containing solutions for continuous blood pressure monitoring via arterial lines
- only saline (0.9% sodium chloride) infusions should be used as the flush solution for arterial lines to minimise the risk of incorrect blood glucose readings and inappropriate insulin administration
- use pressure infusion bags with clear panels to ensure that the fluid label is visible at all times
- report suspected adverse drug reactions associated with glucose solutions on a [Yellow Card](#)
- report medication errors or near misses via local risk management systems and medication errors resulting in patient harm on a [Yellow Card](#)

Review of glucose solutions in arterial lines

Flush fluids are used to maintain the patency of arterial lines when used for the continuous monitoring of blood pressure. The selection and attachment of the wrong flush fluids to arterial lines is a recognised risk and incidents of serious clinical harm have occurred as a result.^{1,2,3,4} When the flush fluid contains glucose and a blood sample is taken from the arterial line, the sample can be contaminated with the glucose from the solution and generate a falsely high blood glucose reading, even after discarding several dead volumes of the fluid. This can result in the inappropriate administration of insulin to the patient and potentially fatal hypoglycaemia.

Discarding dead volume fluid is not sufficient to prevent blood contamination following the use of glucose in the flushing system. When drawing blood samples from patients receiving 5% glucose solution in their flush systems, a discard equal to 5 times the dead space did not prevent clinically significant sample contamination in an open arterial system in a study comparing the performance of three closed system arterial line transducer sets with their partner open systems.⁵

The National Patient Safety Agency issued a rapid response report to highlight these risks in 2008.³ The MHRA conducted a review of the risks associated with inappropriate flush fluid use and subsequently published a [Drug Safety Update article in July 2012](#) (republished in 2014).

More recently, the Healthcare Safety Investigation Branch (HSIB) highlighted the importance of using the appropriate flush fluid in its report [published in 2022](#). Following this HSIB report, we want to remind healthcare professionals about this risk and note that the use of pressure infusion bags with clear panels provides an additional layer of risk mitigation against use of an incorrect flush fluid by enabling users to easily check the label.

Report suspected reactions and medication errors

Please continue to report suspected adverse drug reactions to the Yellow Card scheme.

Healthcare professionals, patients, and caregivers are asked to submit reports using the Yellow Card scheme electronically using:

- the [Yellow Card website](#)
- the Yellow Card app; download from the [Apple App Store](#) or [Google Play Store](#)
- some clinical IT systems for healthcare professionals (EMIS, SystmOne, Vision, MiDatabank, and Ulysses)

When reporting, please provide as much information as possible, including information about batch numbers, medical history, any concomitant medication, onset timing, treatment dates, and product brand name.

Article citation: Drug Safety Update volume 16, issue 10: May 2023: 2.

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3. Hill K. [New guidance issued following problems with infusions and sampling from arterial lines](#). BACCN Nursing in Critical Care 2008: volume 13, page 318.
4. Healthcare Safety Investigation Branch (HSIB), 2022. [The use of an appropriate flush fluid in arterial lines](#).
5. Brennan KA and others. [Reducing the risk of fatal and disabling hypoglycaemia: a comparison of arterial blood sampling system](#). British journal of Anaesthesia 2010: volume 104, pages 446 to 451.

Febuxostat: updated advice for the treatment of patients with a history of major cardiovascular disease

Caution is required if prescribing febuxostat in patients with pre-existing major cardiovascular disease, particularly, in those with evidence of high urate crystal and tophi burden or those initiating urate-lowering therapy.

This article replaces advice issued in [Drug Safety Update published in July 2019](#).

Advice for healthcare professionals:

- in patients with pre-existing major cardiovascular diseases, febuxostat therapy should be used cautiously, particularly in those with evidence of high urate crystal and tophi burden or those initiating urate-lowering therapy
- following initiation of febuxostat, prescribers should titrate the febuxostat dose to minimise gout flares and inflammation
- note that clinical guidelines for gout (see, for example, [NICE guideline 219 – Gout: diagnosis and management](#)) recommend that allopurinol should be offered as first-line treatment for people with gout who have major cardiovascular disease
- report suspected adverse drug reactions associated with febuxostat to the [Yellow Card scheme](#)

Advice for healthcare professionals to give to patients and caregivers:

- febuxostat is used to treat gout by reducing an excess of a chemical called uric acid (urate) in the body, which prevents attacks of gout in the long term; it can also be used to treat and prevent high blood levels of uric acid that may occur when you start to receive chemotherapy for blood cancer
- there are new recommendations to healthcare professionals about use of febuxostat in patients with previous heart problems
- if you currently have or have previously had heart failure, heart problems or stroke, it is recommended to talk to your doctor before taking febuxostat
- no action is needed from patients already on febuxostat, but talk to a healthcare professional if you are concerned

About febuxostat and treatment of gout

Febuxostat, at doses of 80 milligrams (mg) and 120mg, is indicated for treatment of chronic hyperuricaemia in conditions where urate deposition has already occurred (including a history, or presence, of tophus or gouty arthritis). Febuxostat at a dose of 120mg is indicated for the prevention and treatment of hyperuricaemia in adult patients undergoing chemotherapy for haematologic malignancies at intermediate to high risk of tumour lysis syndrome. The advice in this article relates to treatment of chronic hyperuricaemia (gout).

Gout is a type of inflammatory arthritis caused by monosodium urate crystals forming inside and around joints, causing sudden flares of severe pain, heat, and swelling. Gout has been associated with an increased risk of cardiovascular disease and cardiovascular mortality. Gout flares may occur during initiation of urate-lowering treatment due to changing serum uric acid levels resulting in mobilisation of urate from tissue deposits. Management of gout flares may require use of non-steroidal anti-inflammatory drugs, colchicine, or oral corticosteroids.

Warnings regarding cardiovascular disease

In July 2019, we advised [healthcare professionals to avoid febuxostat treatment](#) in patients with pre-existing major cardiovascular disease (for example, myocardial infarction, stroke, or unstable angina), unless no other therapy options were appropriate. This followed a review of the findings from a phase 4 clinical trial (the CARES study¹) in patients with gout and a history of major cardiovascular disease. The CARES study showed a higher risk for cardiovascular-related death and for all-cause mortality in patients assigned to febuxostat than in those assigned to allopurinol.

A further trial has now been concluded on the cardiovascular safety of febuxostat, the FAST study.² The FAST study was conducted in patients in the UK, Denmark, and Sweden who had at least one cardiovascular risk factor and had already been treated with allopurinol for a median duration of 6 years; additionally, serum urate levels were controlled with dose-optimised allopurinol before randomisation. The FAST study concluded that febuxostat was non-inferior to allopurinol therapy with respect to the primary cardiovascular endpoint, and, unlike the CARES study results, that long-term use was not associated with an increased risk of death or cardiovascular death compared to allopurinol.

Following a review of the FAST study findings and advice from the [Pharmacovigilance Expert Advisory Group](#) of the Commission on Human Medicines, the product information for febuxostat has been updated to include the results. The product information retains the warning for cardiovascular disorders and now advises that treatment of patients with pre-existing major cardiovascular diseases with febuxostat should be exercised cautiously.

In particular, treatment should be exercised cautiously in patients with pre-existing major cardiovascular diseases with evidence of high urate crystal and tophi burden or those initiating urate lowering therapy. Prescribing clinicians should titrate febuxostat appropriately to minimise gout flares following initiation, thus minimising additional inflammation.

We also note that clinical guidelines for gout (for example, [NICE guideline 219 – Gout: diagnosis and management](#) which has been updated since the time of the FAST study publication), state that allopurinol should be offered as first-line treatment to people with gout who have major cardiovascular disease (for example, previous myocardial infarction or stroke, or unstable angina).

Detailed study findings

The CARES study

Further information on the design and findings of the CARES study can be found in the [Drug Safety Update issued July 2019](#) and in the published findings.¹ In summary, the CARES study was a phase 4, randomised, double-blind, non-inferiority trial in which patients with gout and a history of major cardiovascular disease from the USA, Canada and Mexico. A total of 6190 patients were randomised to receive febuxostat or allopurinol and were followed for a median of 32 months.

The primary major adverse cardiovascular events (MACE) endpoint occurred at similar rates in the febuxostat and allopurinol treatment groups (10.8% versus 10.4% of patients, respectively; hazard ratio (HR) 1.03, 95% confidence interval (CI) 0.87 to 1.23). In secondary analysis, the incidence of cardiovascular deaths was higher in the group assigned to febuxostat than in the group assigned to allopurinol (4.3% versus 3.2%, respectively; HR 1.34, 95% CI 1.03 to 1.73). The incidence of all-cause mortality was also higher in patients assigned to febuxostat than in those assigned to allopurinol (7.8% versus 6.4% respectively; HR 1.22, 95% CI 1.01 to 1.47), which was mainly driven by the higher rate of cardiovascular deaths in the febuxostat group.

The FAST study

The FAST study was a prospective, randomised, open label, blinded-endpoint, non-inferiority trial that evaluated the risk of cardiovascular events with febuxostat versus allopurinol in 6,128 patients with gout in the UK, Denmark, and Sweden who had at least one cardiovascular risk factor.²

Patients had been receiving urate-lowering therapy with allopurinol at inclusion for a median duration of 6 years. Prior to randomisation they had received dose-optimised allopurinol to lower urate concentration to European Alliance of Associations for Rheumatology (EULAR) target level of below 0.357 mmol/L (below 6 mg/dL).

The FAST study results showed that febuxostat was non-inferior to allopurinol therapy with respect to the primary cardiovascular endpoint (composite of hospitalisation for non-fatal myocardial infarction or biomarker-positive acute coronary syndrome; non-fatal stroke; or cardiovascular death), with an on-treatment incidence of 5.6% for febuxostat vs 7.9% for allopurinol (HR 0.85, 95% CI 0.70 to 1.03, $p < 0.0001$, non-inferior). Secondary endpoints for febuxostat versus allopurinol on-treatment included cardiovascular death 2% vs 2.7% respectively, HR 0.91 (0.66–1.27), and all cause death 3.5% vs 5.7% respectively, HR 0.75 (0.59–0.95) $p < 0.0001$, non-inferior.²

There were differences between the FAST and CARES study populations and protocols, which need to be considered when comparing and contrasting the results of these trials, including:

- febuxostat-treated patients were older in FAST than in CARES (mean age 71 years (standard deviation [SD] 6.4) versus median age 64 years (interquartile range [IQR] 58 to 71 years, respectively)
- 33.4% of patients in FAST had a history of cardiovascular disease compared to 100% patients in CARES

- zero patients in FAST were initiating urate-lowering therapy compared to 33.7% of patients in the CARES study
- patients in the FAST study at baseline just prior to randomisation had a mean serum urate level of 5mg per dL (0.297 mmol/L) compared to 8.7mg per dL (0.517mmol/L) in CARES
- at baseline fewer patients in the FAST study had tophi compared to CARES (9.8% versus 21.6% respectively in febuxostat-treated patients).

As such, febuxostat treatment of chronic hyperuricaemia in patients with pre-existing major cardiovascular diseases should be exercised cautiously, with particular caution in patients with evidence of high urate crystal and tophi burden or those initiating urate lowering therapy.

Report via Yellow Card

Healthcare professionals, patients, and caregivers are asked to submit reports using the Yellow Card scheme electronically using:

- the [Yellow Card website](#)
- the Yellow Card app; download from the [Apple App Store](#) or [Google Play Store](#)
- some clinical IT systems for healthcare professionals (EMIS, SystemOne, Vision, MiDatabank, and Ulysses)

When reporting suspected adverse drug reactions, please provide as much information as possible, including information about medical history, any concomitant medication, onset timing, and treatment dates. When reporting for a biological medicine or vaccine, please ensure that you provide the brand name (or product licence number and manufacturer), and the specific batch number.

Yellow Card biobank launch

We note that the MHRA has recently launched the [Yellow Card biobank](#) in a joint venture with Genomics England. The pilot phase will start with allopurinol and rare severe skin reactions, including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN). Other topics of focus for the pilot phase will be confirmed in due course.

Those interested in getting involved should visit the [Yellow Card biobank page](#). Individuals who have previously submitted a Yellow Card report relating to the pilot topics may also be asked if they would like to participate. In instances where a healthcare professional has reported on behalf of a patient, they may be asked to help contact the affected patient to see if they wish to be involved.

Article citation: Drug Safety Update volume 16, issue 10: May 2023: 3.

References

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2. Mackenzie IS and others. [Long-term cardiovascular safety of febuxostat compared with allopurinol in patients with gout \(FAST\): a multicentre, prospective, randomised, open-label, non-inferiority trial](#). Lancet 2020: volume 396: pages 1745 to 1757.

Letters and medicine recalls sent to healthcare professionals in April 2023

National Patient Safety Alerts

Removal from service of Philips Health Systems V60 and V60 Plus ventilators

On 18 May 2023, we issued a [National Patient Safety Alert to instruct that all Philips V60 and V60 Plus ventilators should be permanently removed from use in the UK healthcare system](#) by no later than 30 September 2023. This is due to electrical issues with the devices that may, in rare instances, cause them to shut down unexpectedly.

V60 and V60 Plus devices are used in hospitals. Depending on the model, these ventilators can provide non-invasive and continuous positive airway pressure treatment to patients in critical-care, respiratory support units and high-dependency units.

The safety concern relates to several electrical faults in the devices. These faults can result in an unexpected shutdown leading to loss of ventilation – in some instances without a warning alarm to alert users that the machine is shutting down. If unnoticed by healthcare professionals, ventilation failure can have severe consequences for patients including hypoxia, which can result in long-term cognitive impairment. There is also a risk of death if a patient is without ventilation for a sustained period.

If there is a risk of severe patient harm due to a lack of alternative ventilators, providers may continue to use affected ventilators until 30 September 2023, but only with appropriate risk mitigation measures in place – see [Risk assessment and additional patient monitoring requirements if temporary use of affected devices cannot be avoided](#). However, all V60 range ventilators must be removed from service with replacement devices in use by 30 September 2023.

This action follows a comprehensive scientific and technical review, and advice from the independent Interim Devices Working Group (IDWG), along with input from clinical experts and key partners across the healthcare system.

We are working closely with the Department of Health and Social Care, which will be able to provide information on arrangements to supply replacement ventilators to any hospitals where staff feel they are needed, to ensure capacity is maintained.

Recall of Emerade 500 micrograms and Emerade 300 micrograms auto-injectors, due to the potential for device failure

On 9 May 2023 we issued a [National Patient Safety Alert](#) to support the recall from patients of all unexpired Emerade 500 micrograms and Emerade 300 micrograms adrenaline auto-injectors (also referred to as pens). This is due to an issue identified

during testing where some auto-injectors failed to deliver the product or activated prematurely after they had been dropped (the 1-metre free-fall study).

It is unclear what impact this has on auto-injectors in clinical use, however as a precautionary measure and owing to the inability to identify this issue before the auto-injectors are used, all Emerade auto-injectors are being recalled in the UK.

Healthcare professionals are asked to:

1. Stop supplying the impacted products immediately, quarantine remaining stock and return using their supplier's approved process.
2. Identify patients who have been supplied with Emerade 500 micrograms and Emerade 300 micrograms auto-injectors and ensure that they are reviewed by their prescriber to determine whether their adrenaline auto-injector prescription is still appropriate and in line with existing guidance.
3. Immediately inform patients and carers to request a new prescription to replace each Emerade 500 micrograms and Emerade 300 micrograms auto-injector with an adrenaline pen in an alternative brand. Epipen 300 micrograms or Jext 300 micrograms are appropriate alternatives to Emerade 500 micrograms. Dosing recommendations are available in the Summary of Product Characteristics (SmPC) and should be followed.
4. Inform patients to return Emerade auto-injectors to any pharmacy after they have obtained a total of 2 equivalent-strength adrenaline pens in an alternative brand.

General Practitioners (GPs) and Pharmacy Teams are asked to send the linked letter [Advice for patients who have been prescribed Emerade auto-injectors](#) to all patients and carers who have been prescribed Emerade auto-injectors. For further information on safe and effective use of adrenaline auto-injectors please refer to the MHRA's [Adrenaline Auto-Injectors \(AAs\) safety campaign](#).

Letters

In April 2023, the following letters were sent or provided to relevant healthcare professionals:

- [Caprelsa \(vandetanib\): restriction of indication](#)
- [Ketalar 10 mg/ml Injection 20ml vial: Temporary supply of an unlicensed imported product from Switzerland](#)
- [Naseptin Nasal Cream: Caution advised when prescribing and dispensing due to reformulation to remove allergen](#)
- [Brabio \(glatiramer acetate\) 20 mg/ml solution for injection, pre-filled syringe, once daily dosage: Patient information leaflet update](#)

Medicine Recalls and Notifications

In April 2023, recalls and notifications for medicines were issued on:

[Company led medicines recall: Spectrum Therapeutics UK, Canopy AKH 22 Dried Cannabis 5g \[unlicensed medicine\], CLMR \(23\)A/04.](#) Issued 20 April 2023. The importer and distributor of this product has informed the MHRA of reports that following tests, the microbial limit for Total Microbial Aerobic Count (TAMC) has been found to exceed the predefined limit of 200 CfU/g as per the product specification fixed according to Pharm. Eur. Monograph 5.1.4 (inhalation use). Therefore, these batches are being recalled as a precautionary measure. Spectrum Therapeutics UK is able to fully trace the onward distribution by their customers.

[Class 4 Medicines Defect Information: Sandoz Limited, Co-amoxiclav 125/31.25mg/5ml, 250/62.5mg/5ml powder for oral suspension, EL \(23\)A/14.](#) Issued 20 April 2023. Sandoz limited has informed the MHRA that the products mentioned in this notification are not sugar free despite the carton stating 'sugar free'. The 'sugar free' text was added to the carton in December 2008 in error. All batches supplied since December 2008 have contained a very small quantity of sugar originating from the flavouring. The contained sugars are dextrose and maltodextrin, which are both composed of glucose. However, for a small cohort of patients the product may not be suitable. There is no risk to product quality as a result of this issue, and the affected batches are not being recalled. Healthcare professionals are advised to inform patients about the error when dispensing subsequent batches or in discussion with patients who may have concerns related to sugar intake or glucose control, where appropriate.

Medical Device Safety Information

We recently published a Device Safety Information page on the following topics:

[NuVasive Specialized Orthopedics \(NSO\) PRECICE Titanium Systems: UK Suspension Lifted, DSI 2023/006](#)

In 2021 all PRECICE Titanium System devices for orthopaedic surgery were voluntarily suspended from use while additional testing was carried out for biological safety and for use in under 18s. The MHRA has conducted a thorough assessment of technical and biological safety information provided by the manufacturer NuVasive Specialized Orthopedics (NSO) and is satisfied that the PRECICE Titanium subset of devices can now be used in adults in the UK.

PRECICE Titanium systems Intra-Medullary Limb Lengthening (IMLL), Short, Unyte and Freedom can now be appropriately selected for use in surgery. Healthcare professionals should follow the actions set out in the manufacturer's Field Safety Notice. The PRECICE devices should only be implanted in accordance with the Manufacturer instructions For Use. These devices have not been validated by NSO for use in children and adolescents and any use of this device in these populations is considered 'off-label' use.

The CE marks for PRECICE Biodur systems (Stryde and Plate) have not been reinstated and all PRECICE Biodur systems (Bone Transport, Stryde and Plate) remain suspended from the UK market.

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