

## 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/government/organizations/medicines-and-healthcare-products-regulatory-agency/email-signup>

First, we inform of the new pre-vaccination checklist for the yellow fever vaccine. The checklist aims to ensure vaccination is indicated for the intended travel destination and enable vaccinators to identify existing contraindications or precautions in individuals before vaccination.

Next, we provide details of the resupply to the market of Emerade adrenaline auto-injectors and remind healthcare professionals of the important safety precautions when prescribing and advising patients about adrenaline auto-injectors. This advice follows the publication of a report from the Commission on Human Medicines on the effective and safe use of adrenaline auto-injectors for the emergency treatment of anaphylaxis.

On page 9 we summarise recent advice relating to COVID-19 vaccines and medicines published since the October 2021 issue of Drug Safety Update. And on page 11 we include recent letters, recalls and notifications sent to healthcare professionals about medicines.

## Yellow fever vaccine (Stamaril): new pre-vaccination checklist

A standardised pre-vaccination checklist has been introduced to ensure the yellow fever vaccine is indicated for the intended travel destination and to enable vaccinators to identify existing contraindications or precautions in individuals before vaccination.

### Advice for healthcare professionals:

- a yellow fever vaccine is a highly effective vaccine to protect against life-threatening yellow fever infection; for most people the balance between the benefits and possible side effects of the vaccine remains overwhelmingly favourable
- adherence to contraindications (for example, in people with immunosuppression or thymus dysfunction or thymectomy) and precautions (in people aged 60 years or older, infants aged 6 months to 9 months, and pregnant or breastfeeding women) is essential to reduce the risk of very rare but potentially fatal adverse reactions – [see 2019 Drug Safety Update on safety measures](#)
- use the new checklist in vaccination consultations to ensure systematic evaluation of benefits and risks for individual travellers
- the checklist is not a replacement for the full travel health risk assessment by a qualified practitioner and additional checklists or materials may also be used prior to vaccination, depending on clinical guidance
- provide the Patient Information Leaflet and advise patients of the need to seek emergency medical attention if they develop signs or symptoms of a severe reaction following vaccination
- report suspected adverse reactions to the yellow fever vaccine to the [Yellow Card Scheme](#).

### Benefits of the yellow fever vaccine

Yellow fever is a life-threatening viral infection and protective measures against the disease are essential for anyone travelling to an area where there is a risk of infection. Yellow fever vaccine ([Stamaril](#)) is highly effective and is the best way to protect those at risk of disease during travel.

Yellow fever vaccine must only be administered in a registered Yellow Fever Vaccination Centre by registered healthcare professionals who have completed the yellow fever training programme run by [National Travel Health Network and Centre \(NaTHNaC\)](#) in England, Wales and Northern Ireland or [Public Health Scotland](#).

### Very rare adverse reactions associated with yellow fever vaccine

For most people, the balance between the benefits and possible side effects of the vaccine remains overwhelmingly favourable. However, because the vaccine contains a live, weakened strain of the yellow fever virus, adherence to contraindications and precautions is essential to reduce the risk of serious side effects, especially in patients with contraindications due to immunosuppression (congenital or acquired) or thymus dysfunction or removal.

Very rare cases of yellow fever vaccine-associated viscerotropic disease (YEL-AVD) and yellow fever vaccine-associated neurotropic disease (YEL-AND) are important identified risks associated with the yellow fever vaccine. In 2018 to 2019, two events of YEL-AVD with a fatal outcome were reported after yellow fever vaccination in UK. These events led the Commission on Human Medicines to introduce [a series of recommendations to strengthen measures](#) to minimise these risks.

These recommendations included a [letter sent to vaccination clinics in 2019](#), changes to product information (which have now been made), and a standardised pre-vaccination screening checklist, which has now been agreed by the manufacturer and the MHRA.

### **Procedures for vaccination clinics**

Before administration of the yellow fever vaccine, the Summary of Product Characteristics requires that healthcare professionals must ensure that:

1. Yellow fever vaccination is recommended for the intended destination, based on yellow fever endemic status at the time of the travel or if an International Certificate of Vaccination is required; this information is available from the [World Health Organization](#), [NaTHNaC](#) or [Public Health Scotland](#)
2. The traveller has no contraindication for vaccination (such as acquired or congenital immunosuppression, including thymus disorders or thymectomy for any reason, and known immunosuppressive therapies, or are infants younger than 6 months) – see [full contraindications](#)
3. They have explored and thoroughly assessed the risk factors and precautions as listed in the section '[Special warnings and precautions for use](#)' before vaccine administration (for example, people aged 60 years or older, infants aged 6 months to 9 months, and pregnant or breastfeeding women)
4. The traveller is informed of risks associated with vaccination or non-vaccination following the full risk assessment – it is the healthcare professional's responsibility to ensure the patient understands and accepts the risks before vaccination
5. Vaccinees are advised to seek emergency medical attention if they develop signs or symptoms of YEL-AND or YEL-AVD and receive the manufacturer's Patient Information Leaflet, which lists characteristics of these reactions

The newly introduced [Stamaril Yellow Fever vaccine checklist](#) supports this consultation. However, it is not a replacement for the full travel health risk assessment currently undertaken by a qualified practitioner.

## Report suspected reactions to vaccines

Please continue to report suspected adverse reactions to the yellow fever vaccine and other medicines to the [Yellow Card Scheme](#). Submit reports 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 a suspected reaction to a vaccine, please provide the brand name (or product licence number and manufacturer) and the specific batch number. Additionally, when providing patients with details of the vaccine administered, it is good practice to give them details of the brand and batch number. This will allow patients and carers to report suspected reactions more accurately to the Yellow Card Scheme.

Incidents involving the yellow fever vaccine in England, Wales, and Northern Ireland should be reported to NaTHNaC and incidents in Scotland should be reported to Public Health Scotland.

Any medication errors (for example, vaccination of a contraindicated person) that result in harm should be reported via the [Yellow Card Scheme](#). Medication errors in the absence of harm should be reported via local reporting methods.

Report suspected side effects to medicines, vaccines, medical device and test kit incidents used in coronavirus (COVID-19) testing and treatment using the dedicated [Coronavirus Yellow Card reporting site](#) or the Yellow Card app. See the MHRA website for the [latest information on medicines and vaccines for COVID-19](#).

*Article citation: Drug Safety Update volume 15, issue 4: November 2021: 1.*

## **Adrenaline auto-injectors: reminder for prescribers to support safe and effective use**

Emerade 300 and 500 microgram adrenaline auto-injectors have been re-supplied to the market following the implementation of corrective actions – patients and their caregivers should be provided with training and advice specific to their prescribed adrenaline auto-injector.

Follow the advice in the Summary of Product Characteristics for dosing considerations and continue to reiterate to patients the importance of carrying 2 in-date adrenaline auto-injectors with them at all times.

### **Advice for healthcare professionals:**

- Emerade 300 microgram and 500 microgram adrenaline auto-injectors have been re-supplied to the market following the implementation of corrective actions to resolve the issue that caused some devices to fail to activate and deliver adrenaline
- for each adrenaline auto-injector, follow advice in the Summary of Product Characteristics to prescribe appropriate doses for individual patients (see section on dosing considerations)
- remind patients to follow existing advice to carry 2 in-date adrenaline auto-injectors with them at all times and to replace them before they expire
- provide patients and their caregivers with training and advice specific to their prescribed adrenaline auto-injector; encourage them to order a trainer device from the manufacturer to ensure they are familiar with using their auto-injector
- suspected adverse drug reactions or defective medicines should be reported to the [Yellow Card scheme](#)

### **Advice for healthcare professionals to provide to patients:**

- the 300 and 500 microgram strengths of Emerade are being made available again, following corrections made to the auto-injector device
- the Epipen and Jext brands of adrenaline auto-injector in a strength of 300 microgram continue to be suitable alternatives to the Emerade 500 microgram adrenaline auto-injector; this has been confirmed by measurement of adrenaline blood levels following administration
- it is vital to carry 2 in-date adrenaline auto-injectors with you at all times and replace them before they expire
- make sure you and your caregivers know when and how to use your adrenaline auto-injector before you need to use it in an emergency; practice with a training device so you are familiar with how your particular auto-injector works
- always read the Patient Information Leaflet that accompanies your medicines and ask your doctor, nurse, or pharmacist if you have any questions

- you should use your adrenaline auto-injector as soon as you suspect a severe allergic reaction (anaphylaxis), especially any signs affecting your airway (swelling of your tongue or a feeling of constriction in your throat), breathing (wheezing, difficulty in breathing), or your circulation (feeling faint, dizzy, cold clammy skin)
- At first signs of anaphylaxis:
  1. Use an adrenaline auto-injector immediately; do not delay
  2. Call 999, ask for an ambulance, and say ana-phyl-ax-is (even if symptoms appear to be improving after using an auto-injector)
  3. Lie down and raise your legs
  4. Use a second auto-injector if your symptoms haven't improved after 5 minutes
  5. Lying down is important to keep blood flowing to your organs; you can sit up if you are struggling to breathe, but keep your legs elevated as far as possible and lie back down again as soon as you can

## Adrenaline auto-injectors in the UK

Adrenaline auto-injectors are authorised for the emergency treatment of severe acute allergic reactions (anaphylaxis) triggered by allergens in foods, medicines, insect stings or bites, and other allergens, as well as for exercise-induced or idiopathic anaphylaxis.

Adrenaline auto-injectors available in the UK are:

- [Emerade](#)
- [EpiPen](#)
- [Jext](#)

In addition to advice in the Summary of Product Characteristics and Patient Information Leaflet, each brand of adrenaline auto-injector has educational materials available for healthcare professionals and patients. People with allergies and their carers can also use manufacturers' websites to order trainer devices and to sign up for expiry alert services.

## Emerade activation issue

In 2020, Emerade adrenaline auto-injectors were [recalled from patients and pharmacies](#) due to an error in one component that caused some auto-injectors to fail to activate and deliver adrenaline.

The MHRA has reviewed the Marketing Authorisation Holder's results from its investigation into activation failures and the subsequent implementation of corrective actions. The MHRA has confirmed that 300 microgram and 500 microgram strengths of the Emerade auto-injectors can be re-introduced in the UK. In October 2021, a [letter was sent to healthcare professionals](#) to inform them of the reintroduction.

The Emerade 150 microgram auto-injector will not be returning to market at this time, further details will be provided at a later date.

## Report of Adrenaline Auto-injector Expert Working Group

In October 2019, the [Commission on Human Medicines](#) (CHM) endorsed the formation of an Adrenaline Auto-injector Expert Working Group (EWG) to examine a range of cross-cutting areas to support the effective and safe use of adrenaline auto-injectors for the emergency treatment of anaphylaxis. Members of the EWG included representatives from patient groups, allergy charities, the NHS, as well as allergy and immunology medical specialists.

On 11 November 2021, the Group's conclusions and recommendations were made available in a [Public Assessment Report: Recommendations to support the effective and safe use of adrenaline auto-injectors](#). A letter has also been sent to stakeholder organisations so that these recommendations can be implemented.

### Dosing considerations for adrenaline auto-injectors

Each brand of adrenaline auto-injector is available in more than one strength (corresponding to the dose delivered by the device). Broadly, the lower strength is suitable for younger children and the higher strengths suitable for older children and adults. Advice in Section 4.2 of the Summary of Product Characteristics should be followed for recommendations on dose, which are guided principally on age of the patient and their bodyweight.

Only one brand of adrenaline auto-injector (Emerade) is available in a 500 microgram strength, with the other 2 brands being available in a maximum strength of 300 microgram. The labelled strength of adrenaline auto-injectors reflects the dose of adrenaline dispensed by the device in a single injection. However, the amount of adrenaline reaching the bloodstream in a particular time window can differ according to patient-specific and device-specific factors.

In 2015, a [safety review](#) mandated that manufacturers carry out pharmacokinetic/pharmacodynamic studies for adrenaline auto-injectors. Findings from these studies were added to section 5.2 of the Summary of Product Characteristics. These studies found that in healthy people, adrenaline auto-injectors of the same strength but with shorter needles and potentially higher propulsive force (EpiPen and Jext 300 micrograms) delivered more of the adrenaline dose to the bloodstream in the first 30 minutes than did the Emerade 300 microgram auto-injector. As such, the EpiPen or Jext brands of 300 microgram adrenaline auto-injector are both suitable alternatives to the Emerade 500 microgram adrenaline auto-injector.

Further information for prescribers and patients on adrenaline blood level data is included in the report linked above and in the Summary of Product Characteristics for each medicine.

### Report suspected adverse drug reactions

Please report suspected adverse drug reactions (ADRs) or suspected defective medicines to the MHRA through the [Yellow Card scheme](#). For adrenaline auto-injectors details of the strength and batch number should also be included to assist monitoring.

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.

Any suspected non-activated or otherwise defective pens should be retained for investigation and the Marketing Authorisation Holder contacted for advice.

Report suspected side effects to medicines, vaccines, medical device and test kit incidents used in coronavirus (COVID-19) testing and treatment using the dedicated [Coronavirus Yellow Card reporting site](#) or the Yellow Card app. See the MHRA website for the [latest information on medicines and vaccines for COVID-19](#).

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## COVID-19 vaccines and medicines: updates for November 2021

Recent information relating to COVID-19 vaccines and medicines that has been published since the October 2021 issue of Drug Safety Update, up to 12 November 2021.

### Approval of Lagevrio (molnupiravir)

We have [approved Lagevrio \(molnupiravir\)](#), following a rigorous review of its safety, quality and effectiveness by us and the government's independent expert scientific advisory body, the [Commission on Human Medicines](#) (CHM), making it the first oral antiviral for the treatment of COVID-19 to be approved.

Lagevrio (molnupiravir) is safe and effective at reducing the risk of hospitalisation and death in people with mild to moderate COVID-19 who are at increased risk of developing severe disease.

Lagevrio works by interfering with the virus' replication. Based on the clinical trial data, Lagevrio is most effective when taken during the early stages of infection and so we recommend its use as soon as possible following a positive COVID-19 test and within five days of symptoms onset.

Molnupiravir has been authorised for use in people who have mild to moderate COVID-19 and at least one risk factor for developing severe illness. Such risk factors include obesity, older age (>60 years), diabetes mellitus, or heart disease.

For more information about Lagevrio (molnupiravir), see our [Press release](#) and [Decision page](#) which includes the [Summary of Product Characteristics](#) and [Patient Information Leaflet](#).

### Summaries of Yellow Card reporting and other recent MHRA publications

We continue to publish the summaries of the [Yellow Card reporting for the COVID-19 vaccines](#) being used in the UK. The report summarises information received via the Yellow Card scheme and will be published regularly to include other safety investigations carried out by the MHRA under the [COVID-19 Vaccine Surveillance Strategy](#).

We have also recently:

- added Guillain-Barré syndrome (GBS) as a very rare side effect for Vaxzevria (previously COVID-19 Vaccine AstraZeneca) and updated the [Information for Healthcare Professionals](#) and [Information for UK recipients](#)
- updated the [Summary of Product Characteristics](#) sections 4.8 and 5.1 of the Pfizer/BioNTech vaccine for COVID-19 with additional information on potential side effects and vaccine efficacy, and updated section 4 of the [Patient Information Leaflet](#) with possible side effects
- updated the [Summary of Product Characteristics](#) (sections 4.3, 4.4 and 4.8) and [Patient Information Leaflet](#) (section 2 and 4) for COVID-19 Vaccine Janssen

We previously included summaries of latest COVID-19 information, including in the [August 2021](#), [September 2021](#) and [October 2021](#) issues of Drug Safety Update. See [guidance on COVID-19 for all our latest information](#), including after publication of this article.

## Reporting Yellow Cards

Suspected adverse reactions associated with COVID-19 vaccines should be reported to the MHRA through the MHRA's [Coronavirus Yellow Card reporting site](#) or via the Yellow Card app.

As these products are under additional monitoring this includes all suspected ADRs associated with these vaccines. This will allow quick identification of new safety information.

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

You may be contacted following submission of a Yellow Card report so that we can gather additional relevant information for the assessment of the report. These contributions form an important part of our understanding of suspected adverse events.

*Article citation: Drug Safety Update volume 15, issue 4: November 2021: 3.*

# Letters and medicine recalls sent to healthcare professionals in October 2021

## Letters

In October 2021, the following letters were sent or provided to relevant healthcare professionals:

- [Emerade 300 microgram and 500 microgram adrenaline auto-injectors: re-supply to market – important safety information](#) (see accompanying article on page 5)
- [Stamaril \(live attenuated yellow fever vaccine\): reminder of the indication, contraindications, recommendations and warnings for use to ensure appropriate evaluation of risk-benefit before vaccination – Yellow Fever vaccine checklist to be completed prior to administration of each traveller](#) (see accompanying article on page 2)
- [Champix \(varenicline\) - batches to be recalled due to presence of impurity N-nitroso-varenicline above the acceptable intake limit](#)
- Synagis solution for injection (palvizumab): Interim supply of [100mg/1ml Italian stock](#); [50mg/0.5ml Turkish stock](#) to mitigate supply disruption
- [Tukysa \(tucatinib\) 50mg and 150mg film-coated tablets: Interim Supply of French or German/Austrian Stock](#)

We also note the following letter issued to healthcare professionals in November 2021:

- [Forxiga \(dapagliflozin\) 5mg should no longer be used for the treatment of Type 1 Diabetes Mellitus](#)

## Medicine Recalls and Notifications

In October 2021, recalls and notifications for medicines were issued on:

[Company led medicines recall: Glucose 10%w/v 10ml injection \(unlicensed medicine\) and Trometamol 7%w/v injection 5mL \(unlicensed medicine\)](#). Issued 4 October 2021. Batches of Glucose 10% w/v injection 10mL and Trometamol 7%w/v injection 5mL are being recalled due to limited assurance of product sterility. This is a precautionary recall. The affected stock should be quarantined when replacement is available.

[Class 2 Medicines Recall: Tesco Flu-Max All In One Chesty Cough & Cold Powder for Oral Solution Wrafton Laboratories Limited \(trading as Perrigo\) EL \(21\)A/24](#). Issued 12 October 2021. Batches of Tesco Flu-Max all in one chesty cough and cold powder for oral solution are being recalled due to an error on the product sachet. The affected sachets incorrectly state that the product can be used in children 12 years and over, whilst the product information and carton correctly state this product should not be given to children under 16 years old. Stop supplying the batch immediately, quarantine all remaining stock and return to supplier.

[Class 2 Medicines Recall: Pfizer Ltd, Champix \(all strengths\) film-coated tablets, EL \(21\)A/25.](#)

Issued 14 October 2021. Batches of Champix 0.5mg film-coated tablets, 0.5mg + 1mg film coated tablets and 1mg film-coated tablets are being recalled. This is a precautionary measure due to the presence of levels of N-nitroso-varenicline above acceptable levels. Stop supplying the batch immediately, quarantine all remaining stock and return to supplier. Healthcare professionals should advise patients undergoing treatment with Champix to discuss and questions or concerns with their prescriber.

[Company led medicines recall: Irinotecan 200mg/ 260mL in sodium chloride 0.9% w/v intravenous infusion and Infliximab \(Remsima\) intravenous infusion in sodium chloride 0.9%.](#)

Issued 21 October 2021. A single batch of Irinotecan 200mg/ 260mL in sodium chloride 0.9% w/v intravenous infusion and several batches of Infliximab (Remsima) intravenous infusion in sodium chloride are being recalled due to reduced product stability and reduced product sterility respectively. Hospital pharmacies should stop supplying the batch immediately, quarantine all remaining stock and return to supplier once replacement stock is available.

[Class 3 Medicines Recall: Bimatoprost Aspire 0.3mg/ml eye drops, solution in single-dose container, Aspire Pharma Limited, EL \(21\)A/26.](#)

Issued 26 October 2021. Batches of Bimatoprost Aspire 0.3mg/ml eye drops are being recalled due to variability in plastic thickness of the single dose containers. This is a precautionary recall as some patients find the defective containers difficult to squeeze to access the product. Stop supplying the batch immediately, quarantine all remaining stock and return to supplier.

We also note the [recent Class 2 recall \(issued 11 November\) of Cold & Flu Relief Capsules available on general sale.](#) Perrigo are recalling the [listed batches available under various liveries](#) due to an error on the leaflet and carton stating an incorrect maximum daily dose for patients aged 12–15 years. MHRA considered the safety assessment for 12 to 15 year olds who may have taken the incorrect daily dose as very low and there is no evidence of any harm, therefore this recall is not direct to patient level. Retailers and wholesalers have been asked to stop supplying the batches immediately, quarantine all remaining stock and return to supplier.

See [Alerts, recalls and safety information](#) for all recent notices.

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