



## 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>

In our first article we inform healthcare professionals about the harms associated with use of falsified Ozempic and Saxenda products. We ask healthcare professionals to advise their patients using these products to always obtain prescription medicines from a qualified healthcare provider and not to use medicines they suspect are falsified as this may lead to serious health consequences. We also ask healthcare professionals to remain vigilant for symptoms linked to hypoglycaemia in patients who may have obtained a product falsified with insulin.

Second, we advise of the risk of drug interactions with the ritonavir component of Paxlovid and remind prescribers of the need to obtain a detailed patient history of current medications before prescribing Paxlovid, checking for listed and potential drug interactions.

Third, we remind of the need to promote vigilance amongst patients for suspected adverse reactions and safety concerns associated with e-cigarettes and e-liquids and to report them to the Yellow Card scheme.

Our final article provides a summary of recent letters and notifications sent to healthcare professionals about medicines. If you have been forwarded this issue of Drug Safety Update, [subscribe directly via our website](#).

## Ozempic ▼ (semaglutide) and Saxenda (liraglutide): vigilance required due to potentially harmful falsified products

Falsified, potentially harmful Ozempic ▼ and Saxenda products have been found in the UK. We ask healthcare professionals to remind patients using these products to always obtain prescription medicines from a qualified healthcare provider and not to use products they suspect are falsified as this may lead to serious health consequences. We also ask healthcare professionals to remain vigilant for symptoms linked to hypoglycaemia in patients who may have obtained a falsified product containing insulin.

### Advice for healthcare professionals:

- be aware that falsified Ozempic and Saxenda products have been found in the UK, including falsified pens containing insulin, which may lead to patient harm
- remain vigilant for symptoms linked to hypoglycaemia in patients who may have obtained a falsified product and provide appropriate treatment for any patient who may have inadvertently administered insulin via these products
- if you encounter a suspected falsified product, quarantine it and report to the [Yellow Card scheme](#)
- advise patients who are concerned that the pens they have purchased might be falsified that they should not use the pens and report as mentioned above
- Ozempic and Saxenda from legitimate supply chains are unaffected

### Advice for healthcare professionals to give to patients and the public:

- you must not use Ozempic and Saxenda products or pens that you suspect are falsified as this may lead to serious health consequences
- check the Patient Information Leaflet for Ozempic and Patient Information Leaflet for Saxenda to clarify what the genuine pens look like. Do not use any products that appear suspicious – an example image of a fake Ozempic pen is available in the MHRA's advice to the public
- falsified Ozempic and Saxenda pens may contain insulin – seek urgent medical attention if you experience symptoms of low blood sugar, which includes feeling dizzy, sweating or blurred vision; take the suspected fake medicine with you so your doctors know what may have caused this
- if more severe symptoms of low blood sugar occur, such as seizures (fits) and loss of consciousness, call 999 immediately
- if obtaining a private prescription (from a non-NHS prescriber), ensure that this is from authorised sources, such as registered online pharmacies, to avoid the risk of receiving falsified pens or products
- report suspected falsified Saxenda or Ozempic products to the MHRA's [Yellow Card scheme](#)

## Background

[Saxenda](#) (liraglutide) is indicated for weight management in adult patients with obesity or people who are overweight and have at least one weight-related comorbidity. [Ozempic](#) (semaglutide) has been authorised for the treatment of adults with insufficiently controlled type 2 diabetes mellitus. Ozempic is not authorised for weight loss, but is used off-label for that purpose.

We remind healthcare professionals of the advice in the [National Patient Safety Alert of July 2023](#) and a [letter to healthcare professionals](#) on actions to mitigate the supply shortage caused by an increase in demand for these products for licensed and off-label indications.

### **Seizures of falsified products**

Up to October 2023, the MHRA has seized 369 potentially falsified Ozempic pens. None were seized before January 2023. We have also received reports of falsified Saxenda pens that have been obtained by members of the public in the UK through non-legitimate routes (any route that does not require a prescription from a qualified prescribing healthcare professional).

We ask healthcare professionals to remind patients and the public to only obtain prescription-only medicines from legal pharmacies and with a prescription from a qualified healthcare professional.

With any medicines bought outside of the legal supply chain, the contents may not match the ingredients on the label. Pens containing insulin, which have been relabelled as Ozempic, have been intercepted in the UK.

All pharmacies in Great Britain, including those online, must be registered with the General Pharmaceutical Council ([GPhC](#)) and meet their standards for registered pharmacies.

Advise patients that the legitimacy of a pharmacy can be verified by referring to the [GPhC website pharmacy registry](#) and checking that the pharmacy is listed there.

The [MHRA's FakeMeds website](#) also provides tools and resources to direct patients to.

### **Reports of harm**

Up to 20 November 2023, the MHRA has received 16 reports to the Yellow Card scheme of the purchase or use of products supposedly containing semaglutide or liraglutide products that were suspected to be falsified. Some of these reports have now been confirmed as falsified medicines.

Five cases reported that the Saxenda and Ozempic pens were confirmed to be falsified with insulin. Some of the recipients were hospitalised and required urgent care. Serious side effects reported in those hospitalised, including hypoglycaemic shock, indicate that the pens may contain insulin rather than semaglutide.

### **Reporting concerns and side effects**

Healthcare professionals, patients and the public can report suspected falsified products to the [Yellow Card scheme](#). Please include in the report as much detail as possible, including if any side effects were experienced following consumption.

Healthcare professionals should quarantine suspected falsified products and retain the product for testing.

Ozempic is a black triangle medicine and therefore all suspected adverse reactions, even those with the legitimate licensed product, should be reported via the Yellow Card scheme.

Please include in the report as much detail as possible, particularly if a side effect continued or started after treatment was stopped. Information about medical history, any concomitant medication, onset timing, treatment dates, and product brand name and presentation (such as prefilled pen) should also be included.

Report to the Yellow Card scheme electronically using:

- the [Yellow Card scheme 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)

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## **Nirmatrelvir, ritonavir (Paxlovid ▼): be alert to the risk of drug interactions with ritonavir**

There is a risk of harmful drug interactions with the ritonavir component of the COVID-19 treatment Paxlovid ▼ due to its inhibition of the enzyme CYP3A, which metabolises many commonly used drugs. Prescribers should obtain a detailed patient history of current medications before prescribing Paxlovid, checking the Paxlovid product information for known and potential drug interactions.

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

- there is a risk of potentially serious drug interactions with the ritonavir component of Paxlovid leading to increased toxicity from, or reduced effectiveness of concomitant medications
- ritonavir is a potent CYP3A4 inhibitor that acts to boost the plasma levels of the nirmatrelvir component of Paxlovid by preventing its degradation; as many commonly used drugs are metabolised by CYP3A4, the risk of harmful drug interactions with Paxlovid is significant
- drug interactions may also reduce the effectiveness of Paxlovid, in the treatment of COVID-19
- obtain a thorough history of patients' current medications, including over the counter (OTC) medications, herbal remedies and illicit or recreational drug use
- refer to the Paxlovid Summary of Product Characteristics ([SmPC](#)) (especially sections 4.3, 4.4 and 4.5) before prescribing Paxlovid to check for contraindications and potential interactions – links to other resources to assist with this are available below
- remind patients to read the Patient Information Leaflet ([PIL](#)) and to be vigilant for any adverse reactions, seeking medical advice when required
- report suspected adverse drug reactions associated with Paxlovid on a [Yellow Card](#)

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

- Paxlovid is used to treat COVID-19 infection in patients at risk of developing severe disease
- Paxlovid is an antiviral medicine composed of 2 drugs called ritonavir and nirmatrelvir
- ritonavir can affect how other medicines work, potentially leading to harmful effects
- because of this risk, your doctor or healthcare provider should ask you detailed questions about which medicines you are currently taking before prescribing Paxlovid and it is important that you mention all medicines that you use, including over the counter (without prescription) medicines, herbal remedies and any recreational drug use
- it is important not to change or stop taking any medications before discussing this with a healthcare professional
- please read the [leaflet](#) that accompanies your medicine and be vigilant for any side effects
- if you are concerned about a potential side effect after taking Paxlovid or any other medication, seek advice from a healthcare professional and submit a [Yellow Card](#)

## **Risk of adverse drug interactions with Paxlovid**

Nirmatrelvir and ritonavir (Paxlovid 150mg/100mg film-coated tablets) is an anti-viral treatment that is indicated for the treatment of COVID-19 in adults who do not require supplemental oxygen and who are at increased risk of progression to severe COVID-19.

Paxlovid should be given as soon as possible after positive results of SARS-CoV-2 viral testing and within 5 days of onset of symptoms. The approved dose is 300mg nirmatrelvir (two 150mg tablets) with 100mg ritonavir (one 100mg tablet) all taken together, orally twice daily, for 5 days.

Prescribing of Paxlovid to [eligible patients in England](#) has recently transferred from Covid Medicines Delivery Units (CMDUs) to primary care providers. The MHRA sought advice from members of the COVID-19 Therapeutics Expert Working Group (EWG) and Commission on Human Medicines (CHM) in February 2022 about communicating the risks of drug interactions with Paxlovid via a DSU article. The publication of a DSU was supported by members of the CHM and the EWG in the event of Paxlovid deployment becoming more widespread.

The ritonavir component of Paxlovid is not active against SARS-CoV-2 but inhibits the CYP3A-mediated metabolism of nirmatrelvir (the active antiviral), thereby increasing plasma concentrations of nirmatrelvir. It is this CYP3A inhibitory activity of ritonavir that poses a risk of harmful drug interactions with Paxlovid.

Harmful interactions can occur with many medicines. Section 4.3 of the SmPC lists all the drugs with which Paxlovid is contraindicated and must not be co-administered, including commonly-used medicines such as analgesics, antibiotics and antihistamines, and more specialized treatments such as antianginal drugs, anticancer drugs and anticonvulsants. Use of Paxlovid with these medicines may lead to serious or life-threatening side effects.

Section 4.5 of the SmPC lists medicines which may lead to potentially significant interactions with Paxlovid, and where Paxlovid should be considered only if the benefits outweigh the risks.

Healthcare professionals must review these sections of the SmPC in detail before prescribing Paxlovid.

The risks of potential drug interactions when taking Paxlovid, and what actions to take if an adverse event occurs, should be explained to patients by the prescriber. Paxlovid is also contraindicated in patients with hypersensitivities to nirmatrelvir, ritonavir or any of the listed excipients, and in patients with severe renal and / or hepatic impairment. Patients should be reminded to read the Patient Information Leaflet (PIL) and speak to a healthcare professional if they have questions.

## **Resources to assist prescribers of Paxlovid**

There are several online resources available to aid in the safe prescribing of Paxlovid<sup>1</sup>:

[Specialist Pharmacy Service \(SPS\): Using nirmatrelvir and ritonavir \(Paxlovid\) in practice](#) sets out comprehensive information on checking interacting medicines as well

as other safety-related issues. This guidance also includes links to specific patient information, including:

- NHS.UK Medicines A-Z: has a monograph for [Paxlovid](#) that includes a section on '[Taking Paxlovid with other medicines and herbal supplements](#)'.

The SPS clinical enquiry answering service supports primary care healthcare professionals in England with questions about Paxlovid. Contact details can be found via [Medicines Advice contact details – SPS - Specialist Pharmacy Service – The first stop for professional medicines advice](#).

In addition, the University of Liverpool hosts several online resources which provide information about the safe prescribing of Paxlovid, such as the [Liverpool COVID-19 Interaction Checker](#). The University has also created a flowchart to aid prescribers in the identification of potential unsafe prescribing regarding patient concomitant medications. You can access the flowchart by selecting the first link under the heading 'Resources for nirmatrelvir/ritonavir (Paxlovid; 5 day administration)' available on this page: [Liverpool COVID-19 Interactions \(covid19-druginteractions.org\)](#).

## **Report any suspected adverse drug reactions**

Please continue to report suspected adverse drug reactions to Paxlovid via the [Yellow Card scheme](#). Your report will help us safeguard public health. 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, 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.

Footnote:

1. Resources accessed on 6 November 2023. The MHRA is not responsible for the content of external websites.

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## **E-cigarette use or vaping: reminder to remain vigilant for suspected adverse reactions and safety concerns and report them to the Yellow Card scheme**

Healthcare professionals should be vigilant for suspected adverse reactions and safety concerns associated with e-cigarettes and e-liquids, commonly known as vapes. Please report adverse reactions to the Yellow Card scheme and promote vigilance among patients.

The MHRA is responsible for assessing whether the manufacturer or submitter has met the requirements in their notification for nicotine-containing e-cigarettes and e-liquids before the product comes to market. Trading Standards are responsible for enforcing the safety and quality of nicotine-containing e-cigarettes and e-liquids once they have been supplied to the UK market. The MHRA is also responsible for collecting and monitoring information about safety concerns related to these products through the Yellow Card Scheme.

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

- document use of e-cigarette products, commonly referred to as 'vapes' and 'vaping' in the medical records for all patients when taking a medical history (see "Document e-cigarette use in medical records")
- advise patients to be vigilant about suspected adverse reactions that occur after the use of e-cigarettes and e-liquids
- advise patients to purchase and use legally compliant e-cigarette and e-liquid products
- report any suspected adverse reactions or safety concerns to the [Yellow Card Scheme](#) and include as many details as possible to ensure the MHRA can continue to perform safety vigilance

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

- continuous reviews by the Office for Health Improvement and Disparities (OHID) have found that whilst not risk-free, vaping (e-cigarette use) is significantly less harmful than smoking and is one of the most effective tools to help adults quit smoking
- only purchase and use 'notified' products from reputable retailers; check if a product has been notified to the MHRA and meets the minimum requirements for supply in the UK by verifying if the product is present in the [MHRA ECIG Publications List](#) (see "Advice for consumers")
- talk to your doctor, a stop-smoking advisor or another healthcare professional if you experience any side effects or have any concerns about the product you are using
- report any side effects or safety concerns that you have to the [Yellow Card scheme](#) and provide as much information as possible to help the MHRA assess your report

## **E-cigarette use in the UK**

The UK Government's Smokefree 2030 plan for England, which aims to reduce the prevalence of tobacco smoking and its associated harms, encourages adult smokers to seek safer alternatives to smoking. As part of this, a new 'Swap to Stop' scheme has been announced which promotes replacing tobacco cigarettes with e-cigarettes to support smokers to quit.<sup>1</sup>



It is estimated that over 4.3 million adults in the UK use vapes. They contribute to an extra 50,000 - 70,000 smoking quits a year in England. The Government is currently piloting a world first programme to provide 1 million smokers with free vape kits to help them quit.

Evidence reviews by the Office for Health Improvement and Disparities (OHID), and previously Public Health England<sup>2</sup> show that e-cigarettes have been proven to be an effective smoking cessation tool and evidence shows that, in the short and medium term, vaping poses a much smaller overall risk than smoking. However, vaping is not risk free.<sup>3,4</sup> Vaping is not recommended for non-smokers and children and the long-term risks are currently unknown.

In the UK, nicotine-containing e-cigarettes and e-liquids are regulated under the Tobacco and Related Products Regulations 2016 (as amended) which set the minimum requirements for the safety and quality of e-cigarette products.

### **Document e-cigarette use in medical records**

Clinicians should ask about and document the use of e-cigarette products and vaping in the medical records for all patients as they would for smoking. Routine documentation will facilitate any future study on long-term effects of e-cigarettes or vaping using medical records.

Clinicians should routinely document:

- Name and brand of the product or products used
- Type of products (for example, a pre-filled disposable device or an e-liquid used with a refillable device)
- Duration and frequency of use
- Substances vaped (for example, nicotine, cannabidiol [CBD] or psychoactive substances)
- Strength of substances

### **Advice for consumers**

Before a nicotine-containing e-cigarette product can be placed on the market, it must be 'notified' to the MHRA through the e-cigarette notification scheme to ensure that it meets the minimum legal requirements for supply in the UK<sup>5</sup>. Under the regulations, only e-cigarette products with a nicotine concentration of up to 20mg/ml (2%) and a volume of nicotine-containing liquid not exceeding 2ml for pre-filled disposable e-cigarettes, cartridges and pods, or 10ml for e-liquid refills, can be supplied to consumers; any e-cigarettes or e-liquids with a nicotine strength and/or volume exceeding these limits are not legally compliant and are not approved for supply in the UK.

E-cigarettes and e-liquids that have been successfully notified and therefore meet the requirements for supply in the UK are published on the [MHRA ECIG Publications List](#). Consumers can view this list and verify whether a product is notified by searching for the brand and product name or ECID number. Consumers should only purchase

nicotine-containing e-cigarette products that are included on the MHRA Publications List.

## How to report any suspected adverse reactions and safety concerns

Healthcare professionals and members of the public can report any suspected adverse reactions (ADRs) or safety concerns associated with nicotine-containing e-cigarettes and e-liquids to the MHRA via the [Yellow Card website](#). Reporting contributes to the continuous monitoring and safety evaluation of e-cigarettes.

When submitting a Yellow Card report, please provide as much information as possible. The following information is particularly valuable for our assessment of reports:

- name and brand, strength, flavour, and batch number of the product used
- ECID number of the product (this is a 12-digit number that may be printed on the outer packaging or product itself)
- duration and frequency of use
- time to onset of the adverse reaction
- medical history including tobacco use and smoking status, details of any pre-existing respiratory disease, seizure disorders and cardiovascular history

Please include any other relevant information including concomitant medications or substances used.

As of October 2023, the MHRA has received 357 suspected ADR reports associated with nicotine containing e-cigarettes and e-liquids through the Yellow Card scheme and from industry. We routinely publish a summary of this data in our [e-cigarette Analysis Print](#).

*Article citation: Drug Safety Update Volume 17, issue 5: November 2023: 3.*

## References

1. [Smokers urged to swap cigarettes for vapes in world first scheme - GOV.UK \(www.gov.uk\)](https://www.gov.uk)
2. [Nicotine vaping in England: an evidence update including health risks and perceptions, September 2022 \(publishing.service.gov.uk\)](https://publishing.service.gov.uk)
3. [Nicotine vaping in England: 2022 evidence update main findings - GOV.UK \(www.gov.uk\)](https://www.gov.uk)
4. [Electronic cigarettes for smoking cessation - Hartmann-Boyce, J - 2022 | Cochrane Library](#)
5. [Advice for Retailers and Producers - GOV.UK \(www.gov.uk\)](https://www.gov.uk)

## Letters and medicine recalls sent to healthcare professionals in October 2023

A summary of recent letters and notifications sent to healthcare professionals about medicines

### Letters

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

- [Salbutamol 2mg/ml nebuliser solution – temporary supply of unlicensed imported product](#)
- [Guanfacine hydrochloride, Intuniv ▼ 1mg, 2mg, 3mg, 4mg prolonged-release tablets: Expected shortage](#)
- [OctaplasLG infusion 200ml bags \(Blood Group A\) \(Human plasma proteins 57.5mg per ml\): Interim Supply of Germany Stock to Mitigate Supply Disruption](#)
- [Oral isotretinoin ▼: New safety measures following review into sexual and psychiatric adverse reactions](#)

### Medicine Recalls and Notifications

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

[Class 4 Medicines Defect Information: Sandoz Limited, Zinacef powder for solution for injection or infusion vials \(all strengths, including stock in GSK livery\), EL \(23\)A/38](#). Issued on 23 October 2023. Sandoz has detected that information on the diluents in the Patient Information Leaflet (PIL) and Summary of Product Characteristics (SmPC) of cefuroxime offer possibility for both intramuscular (IM) and intravenous (IV) administration. The PIL and SmPC state that cefuroxime sodium is compatible with aqueous solutions containing up to 1% lidocaine hydrochloride. However, dilution with lidocaine is intended only for intramuscular (IM) use. The corrected instructions (for future PILs and SmPCs) are detailed in the alert.

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