



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).

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First, we include advice for healthcare professionals regarding the withdrawal of pholcodine-containing medicines from the market. This article was issued on 14 March, ahead of the March 2023 issue of Drug Safety Update, to align with the timing of the recall of these medicines from the market.

On page 5, we have new measures for prescribers of terlipressin in patients with type 1 hepatorenal syndrome to reduce the risk of serious or fatal respiratory failure and sepsis and septic shock.

On page 10, we summarise recent advice relating to COVID-19 vaccines and medicines published since the February 2023 issue of Drug Safety Update. On page 11, we include recent letters, recalls, 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](https://www.gov.uk/drug-safety-update).

Pholcodine-containing cough and cold medicines: withdrawal from UK market as a precautionary measure

Advice for healthcare professionals regarding the withdrawal of pholcodine-containing medicines from the market.

Advice for healthcare professionals:

- pholcodine-containing cough and cold medicines are being withdrawn from the UK market as a precaution following a review which found that their benefits do not outweigh the increased risk of the very rare event of anaphylaxis to neuromuscular blocking agents (NMBAs) used in general anaesthesia
- ask patients scheduled to undergo general anaesthesia involving NMBAs whether they have used pholcodine-containing medicines, particularly in the past 12 months, and maintain awareness about the potential for perianaesthetic anaphylaxis related to NMBAs
- do not dispense or sell pholcodine-containing medicines – consider recommending appropriate treatment alternatives for patients who present with a new dry cough or who are currently taking pholcodine
- pharmacies should follow the [MHRA Class 2 Medicines Recall Notice](#) to quarantine stock of pholcodine-containing medicines and return it to the manufacturer
- report suspected adverse drug reactions to the [Yellow Card scheme](#)

Advice for healthcare professionals to provide to patients:

- pholcodine-containing cough and cold medicines are being withdrawn from sale as a precaution and will no longer be available from pharmacies
- if you are taking a cough medicine (including tablets and syrups), check the packaging, label or Patient Information Leaflet to see if pholcodine is a listed ingredient – if it is, and you have any questions, you can talk to your pharmacist who can suggest a different medicine suitable for you
- there is evidence that using pholcodine-containing medicines leads to an increased risk of the very rare event of an allergic reaction (anaphylaxis) in patients who receive general anaesthesia involving neuromuscular blocking agents (NMBAs) during surgery
- tell your anaesthetist before you have surgery if you have taken pholcodine, particularly in the past 12 months, or think you may have taken a pholcodine-containing product
- there is no increased risk of allergic reactions, including anaphylaxis, with other allergens following pholcodine use and the absolute risk in patients who have used pholcodine is very small, but patients should talk to a pharmacist, their GP or their surgical team if they have any questions

Review of pholcodine

Pholcodine is an opioid medicine approved in adults and children older than 6 years of age to treat non-productive (dry) cough and, in combination with other active substances, for the treatment of symptoms of cold and influenza.

Previous reviews have examined the link between prior use of pholcodine and an increased risk of anaphylaxis during general anaesthesia involving NMBAs.

The potential for cross-reactivity between pholcodine and NMBAs was added to the product information for pholcodine-containing medicines in January 2022.

The MHRA review considered the cumulative safety information, including the results from the recently completed ALPHO study,¹ which showed that use of pholcodine during the 12 months preceding anaesthesia was significantly associated with an increased risk of perianaesthetic anaphylaxis to NMBAs (adjusted odds ratio = 4.2; 95% CI 2.5 to 6.9). Data on the risk related to the use of pholcodine beyond the period of 12 months was not available from this study, although data from an earlier study in Norway suggest that the very small increased risk may persist for up to 3 years.²

The [Commission on Human Medicines \(CHM\)](#) advised that there is sufficient overall evidence for an association with pholcodine, although the absolute risk of anaphylaxis remains very small in patients who have taken pholcodine. Anaphylaxis following use of NMBAs is roughly estimated as having an overall incidence of fewer than 1 case per 10,000 procedures.³

Given the advice of the CHM, and the lack of identifiable effective measures to minimise the increased risk of anaphylactic reactions to NMBAs, pholcodine-containing products are being withdrawn from the market as a precaution.

Pholcodine-containing products have only been available in the UK for purchase in a pharmacy. Pharmacists should provide advice to those who have any concerns about their medicine or would like to seek advice on alternative medicines or management of their symptoms.

The MHRA scientific review took place alongside a [review conducted by the European Medicines Agency](#), which also concluded that the benefits did not outweigh the risks.

Report suspected adverse drug reactions

Please continue to report suspected adverse drug reactions via 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.

References

1. ClinicalTrials.Gov. [Allergy to Neuromuscular Blocking Agents and Pholcodine Exposure \(ALPHO\) study protocol](#). Accessed March 2023.
2. Florvaag E and others. [IgE-sensitization to the cough suppressant pholcodine and the effects of its withdrawal from the Norwegian market IgE-sensitization to the cough suppressant pholcodine and the effects of its withdrawal from the Norwegian market](#). Allergy 2011; 66: 955–960.
3. [Anaesthesia, Surgery and Life-Threatening Allergic Reactions. Report and findings of the Royal College of Anaesthetists' 6th National Audit Project: Perioperative Anaphylaxis](#). Published May 2018. Accessed March 2023.

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Terlipressin: new recommendations to reduce risks of respiratory failure and septic shock in patients with type 1 hepatorenal syndrome

New recommendations following a recent clinical trial which found that in patients with type 1 hepatorenal syndrome terlipressin may cause serious or fatal respiratory failure at a frequency higher than previously known, and that terlipressin increases the risk of sepsis and septic shock.

Consider the individual benefits and risks for patients with type 1 hepatorenal syndrome when initiating terlipressin treatment, especially for those with severe renal or hepatic impairment and monitor all patients closely during terlipressin treatment. This advice is not relevant to use of terlipressin for bleeding oesophageal varices.

Advice for healthcare professionals:

- findings of the [CONFIRM trial](#) showed terlipressin to be effective at reversing type 1 hepatorenal syndrome, but also showed that patients who received terlipressin were more likely to die by day 90 (largely due to respiratory disorders) than those who received placebo
- there were also more serious respiratory events and cases of sepsis or septic shock in patients who received terlipressin than in those who received placebo
- since both advanced renal impairment and advanced liver impairment were risk factors for poorer outcomes in patients with type 1 hepatorenal syndrome:
 - avoid terlipressin in those with advanced renal dysfunction (baseline serum creatinine at or above 442 $\mu\text{mol/L}$ (5.0 mg/dL)), unless the benefit is judged to outweigh the risks
 - avoid terlipressin in those with severe liver disease (defined as Acute-on-Chronic Liver Failure (ACLF) grade 3, a Model for End-stage Liver Disease (MELD) score ≥ 39 , or both), unless the benefit is judged to outweigh the risks
- stabilise patients with new-onset breathing difficulties or worsening of existing respiratory disease before administering terlipressin and monitor closely during treatment
- consider a reduction in albumin dose in patients with signs or symptoms of respiratory failure or fluid overload; discontinue terlipressin if symptoms are severe or do not resolve
- monitor patients daily for signs and symptoms of infection
- monitor blood pressure, heart rate, oxygen saturation, serum sodium and potassium levels, and fluid balance; terlipressin may induce myocardial ischaemia and pulmonary vascular congestion, especially in those with pre-existing cardiopulmonary disease
- terlipressin can be administered as a continuous intravenous infusion as an alternative to bolus injection as infusion may be associated with lower rates of severe adverse events than bolus injection

- patients with type 1 hepatorenal syndrome receiving terlipressin should be counselled on the benefits and risks, even if circumstance necessitates that counselling occurs after treatment with terlipressin is given
- this advice is not relevant to use of terlipressin for bleeding oesophageal varices
- report suspected adverse drug reactions associated with terlipressin on a [Yellow Card](#)

Advice for healthcare professions to provide to patients, as well as families and caregivers:

- terlipressin can be used in hospitals for emergency treatment of type 1 hepatorenal syndrome, a life-threatening type of kidney failure in patients with severely impaired liver function
- terlipressin has been linked to breathing difficulties and blood infections when used to treat patients for type 1 hepatorenal syndrome – healthcare professionals will monitor patients receiving terlipressin closely for these risks
- since patients with very severe liver or kidney disease are thought to be at particular risk, we have recommended that these patients should only receive terlipressin if their prescriber feels that the benefits to them outweigh the potential risks
- patients with concerns about their medicines should talk to their healthcare professional
- this advice is not relevant to use of terlipressin for bleeding from dilated veins in the food pipe leading to the stomach (bleeding oesophageal varices)
- report suspected adverse drug reactions associated with terlipressin on a [Yellow Card](#)

About terlipressin

Terlipressin is a synthetic pituitary hormone. It is authorised for treatment of bleeding from dilated veins in the food pipe leading to the stomach (bleeding oesophageal varices) and for emergency treatment of type 1 hepatorenal syndrome (rapidly progressive renal failure in patients with liver cirrhosis (scarring of the liver) and ascites (fluid accumulation in the abdomen)). The advice in this article relates only to use of terlipressin for type 1 hepatorenal syndrome.

Terlipressin acts as a vasopressin analogue that works by reducing portal venous pressure in the liver, in patients with portal hypertension, and also contributes to improved blood circulation in the kidney helping to restore renal function.

Findings of the CONFIRM trial

The [CONFIRM trial](#)¹ was a phase 3 clinical trial conducted in the USA and Canada, comparing the efficacy of terlipressin plus albumin with that of placebo plus albumin in the treatment of type 1 hepatorenal syndrome. A total of 300 patients underwent randomisation — 199 were assigned to the terlipressin group and 101 to the placebo group.

The primary endpoint of the CONFIRM trial was verified reversal of type 1 hepatorenal syndrome. The study showed that the proportion of patients who had verified reversal of hepatorenal syndrome was significantly higher in the terlipressin group than in the placebo group (63 patients (32%) versus 17 patients (17%); $p=0.0006$).

Mortality up to 90 days was measured as a secondary outcome. By day 90, deaths had occurred in 101 patients (51%) in the terlipressin group and in 45 patients (45%) in the placebo group. The increased mortality at 90 days in the terlipressin group was driven by respiratory disorders, with 22 deaths (11%) due to respiratory disorders in the terlipressin group and 2 deaths (2%) in the placebo group.

The most commonly reported respiratory adverse events in the terlipressin group were respiratory failure, dyspnoea, and pulmonary oedema. These events were reported at a higher frequency than is currently indicated in the product information. The frequency of these events is now evaluated as very common for respiratory failure and dyspnoea and common for pulmonary oedema.

Furthermore, in the time period up to 30 days after the end of treatment, cases of respiratory failure and acute respiratory failure were higher in the terlipressin group than in the placebo group (20 patients (10%) versus 3 patients (3%) for respiratory failure; 8 patients (4%) versus 2 patients (2%), respectively, for acute respiratory failure).

There were also more cases of sepsis; with 14 patients (7%) in the terlipressin group experiencing serious adverse events (SAEs) related to sepsis and septic shock versus none in the placebo group. Eight of these 14 patients who developed sepsis or septic shock in the terlipressin group died due to the event.

Recent review of benefits and risks

A [recent European review](#) into the benefits and risks of terlipressin treatment, which was triggered by the CONFIRM trial findings, concluded that new measures were required to reduce the risk of respiratory failure and sepsis when terlipressin is used in patients with type 1 hepatorenal syndrome. The Pharmacovigilance Expert Advisory Group of the UK's [Commission on Human Medicines](#) agreed with the recommendations, while also highlighting the benefits of terlipressin treatment when an appropriate assessment of the benefits and risks has been made.

Changes will therefore be made to the product information for terlipressin medicines authorised for type 1 hepatorenal syndrome to note the new risk minimisation measures and information on risks. A letter has also been sent to UK healthcare professionals.

Risk factors

The review confirmed that terlipressin remains a highly effective treatment for type 1 hepatorenal syndrome but identified some risk factors that should be considered by prescribers when treatment decisions are made.

The review identified patients with severe renal impairment (in this review, defined as patients with baseline serum creatinine above 5 mg/dl) as being at reduced likelihood of response to terlipressin as well as at increased risk of death. A post-hoc subgroup analysis of the CONFIRM trial identified patients with severe renal impairment (in this review, defined as patients with baseline serum creatinine above 5 mg/dl) and severe reduction in liver function (in particular patients with ACLF grade 3 or a MELD score ≥ 39) as having a reduced likelihood of response to terlipressin as well as an increased risk of developing respiratory failure and fluid-overload-related serious adverse events and of death.

An assessment of benefits and risks for the individual patient should be made when deciding on appropriate treatment in patients with these risk factors.

It was acknowledged that the doses of albumin given in the CONFIRM trial were higher than would usually be advised in European guidelines and this may have contributed to fluid overload and the respiratory events seen. The dose of albumin should therefore be considered if signs of respiratory failure or fluid overload arise.

Method of administration

Continuous infusion has been added to the product information as an alternative method of administration to bolus injection.

Continuous infusion has been recommended within [the European Association for the Study of the Liver \(EASL\) guidelines](#) for some time and a small amount of literature suggests that this method is associated with a better safety profile and has a more stable lowering effect on portal pressure than bolus administration by avoiding high peak plasma concentrations of terlipressin. While the literature is insufficient to suggest that continuous infusion would lower the rate of respiratory events specifically, the evidence is sufficient to recommend this as an alternative method of administration.

Report suspected reactions on a 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, SystmOne, 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.

References

1. Wong F and others. [Terlipressin plus Albumin for the Treatment of Type 1 Hepatorenal Syndrome](#). *New England Journal of Medicine* 2021; volume 384, pages 818 to 828.

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COVID-19 vaccines and medicines: updates for March 2023

Summaries of Yellow Card reporting

Recent information relating to COVID-19 vaccines and medicines that has been published since the February 2023 issue of Drug Safety Update, up to 21 March 2023.

On 8 March 2023 we published the summary report of [Yellow Card reporting for the COVID-19 vaccines](#). This report covers the period up to and including 22 February for COVID-19 vaccines used from the beginning of Autumn 2022.

The Commission on Human Medicines (CHM) has advised that given the end of the Autumn 2022 booster campaign and the stable safety profile of the COVID-19 vaccines, the MHRA should transition to routine data publication and communication of safety concerns for COVID-19 vaccines. The report published 8 March 2023 is therefore the last regular publication of the Summary of Yellow Card reporting for COVID-19 vaccines.

This will also be the last regularly scheduled article in Drug Safety Update of recent COVID-19 vaccines and medicines advice.

Robust safety monitoring and surveillance of any COVID-19 vaccines used in the UK will continue, along with timely communication on any updated safety advice when needed. Additionally, monthly updates of Adverse Drug Reaction (ADR) data will continue with the new interactive [COVID-19 vaccine reports](#).

We would ask anyone who suspects they have experienced a side effect linked with their COVID-19 vaccine or medicine to report via the [Yellow Card website](#).

Other recent MHRA updates on COVID-19 vaccines and medicines:

We have also recently:

- [authorised](#) a new version of the Moderna ‘bivalent’ COVID-19 vaccine (Spikevax) that targets both the original strain of SARS-CoV-2 and the Omicron BA.4 and BA.5 sub-variants
- updated the Summary of Product Characteristics and Patient Information Leaflet to reflect the COVID-19 Janssen vaccine was converted to a full marketing authorisation. Please see the [Decision page](#) on our website which has more details about the COVID-19 Vaccine Janssen

See [guidance on COVID-19 for all our latest information](#), including after publication of this article.

We have included summaries of the latest COVID-19 information being issued by the MHRA since January 2021, including in the [December 2022](#), [January 2023](#) and [February 2023](#) issues of Drug Safety Update.

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Letters and medicine recalls sent to healthcare professionals in February 2023

Letters

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

- [Mylotarg \(gemtuzumab ozogamicin\) 5mg powder for concentrate for solution for infusion: interim supply from US](#)
- [Onasemnogene abeparvovec \(Zolgensma ▼\): fatal cases of acute liver failure](#)
- [ONIVYDE pegylated liposomal 4.3 mg/ml concentrate for dispersion for infusion Interim Supply of Irish packs \(common pack for Republic of Ireland and Northern Ireland\) to Mitigate Supply Disruption](#)
- [ADAKVEO ▼ \(crizanlizumab\): Phase III study \(CSEG101A2301\) shows no superiority of crizanlizumab over placebo](#)

Medicine Recalls and Notifications

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

[Class 4 Medicines Defect Information: Reckitt Benckiser Healthcare \(UK\) Limited, Lemsip Max Cold and Flu Capsules, EL \(23\)A/04](#). Issued 22 February 2023. A typographical error has been identified on the end flap of the outer carton of some batches of Lemsip Max Cold & Flu Capsules. The content of paracetamol per capsule was stated as 500g (grams) instead of 500mg (milligrams). The paracetamol content of each capsule is correctly stated in Patient Information Leaflet (PIL). There is no risk to product quality and/or efficacy.

[Class 4 Medicines Defect Information: Atnahs Pharma UK, Zestoretic 20mg/12.5mg Tablets, EL \(23\)A/05](#). Issued 27 February 2023. The Patient Information Leaflet (PIL) packaged in certain batches of Zestoretic 20mg/12.5mg Tablets contains outdated safety information. There is no risk to product quality as a result of this issue. Healthcare professionals are advised to exercise caution when dispensing the affected batch (batch number SB012, expiry date April 2024). Where possible, please provide patients with an [updated copy of the PIL](#) and remind them to read the leaflet in its entirety before using the medicine.

[Company led medicines recall: Vertical Pharma Resources Ltd T/A IPS Pharma, Levothyroxine Oral Suspension \(Various Strengths\) \[unlicensed medicine\], CLMR\(23\)A/03](#). Issued 27 February 2023. IPS Pharma is recalling specific batches of levothyroxine oral suspension from pharmacies and impacted patients due to the concentration of levothyroxine being greater than the amount stated on the label. The products are supplied to a limited number of patients, and the manufacturer can fully trace the product's distribution.

Medical Device Safety Information

A Device Safety Information page was published in February 2023 on the following topic:

[BD BodyGuard MicroSets and residual ethylene oxide: devices may continue to be used to treat paediatric patients 5kg and above, DSI/2023/004](#)

Ethylene oxide (EO) is a gas commonly used for sterilisation of different types of medical devices. The sterilisation process consists of a number of highly controlled and monitored stages, including the removal of ethylene oxide after treatment. The amount of residual EO that is allowed has been set by the international standard ISO 10993-7:2008 according to contact time of the medical device with the person. These allowable limits were selected to ensure that any residual levels present on the medical device after sterilisation pose minimal risk. EO is a volatile chemical and following sterilisation, the presence of EO further decreases over time.

As a precautionary measure, following an MHRA assessment of currently available data on EO levels, alternative devices to the BD BodyGuard Microsets should be sought in users of 5kg bodyweight and below. This follows an amendment to the international standard which sets out the applicability of allowable limits of EO for neonates and infants on medical devices. The MHRA is not aware of any specific safety concerns with regards to the use of these devices. The manufacturer is currently working to assess whether the residual levels of EO are in line with amended limits for low weight children.

For all the latest safety notices from the MHRA on drugs and medical devices, see [Alerts and recalls for drugs and medical devices](#).

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