The Consumer Healthcare Association

20 March 2023

Pholcodine-containing medicinal products no longer available on the UK market

Dear Healthcare professional,

Following a review by the Medicines and Healthcare products Regulatory Agency (MHRA), the Marketing Authorisation Holders (MAHs) of medicines containing pholcodine, would like to inform you of new safety information resulting in a precautionary withdrawal from the UK market and a recall of all batches for the products listed in the table in Appendix I.

Summary

- **Use of pholcodine preceding anaesthesia with neuromuscular blocking agents (NMBAs) has been linked to an increased risk of perianaesthetic anaphylactic reaction to NMBAs.**
- **No effective measures have been identified to minimise this risk to an acceptable level in patients exposed to pholcodine-containing medicinal products.**
- **As a precaution, pholcodine-containing medicinal products will no longer be available on the UK market.**
- **Pholcodine-containing products have only been available in the UK for purchase in a pharmacy. Pharmacists should provide advice to people who have any concerns about their medicine or would like to seek advice on alternative options or management of their symptoms. The absolute risk in patients who have used pholcodine is very small.**
- **In case of anaesthesia requiring administration of NMBAs, healthcare professionals should check whether patients think they have used pholcodine-containing medicinal products, especially in the past 12 months and, if so, maintain awareness about the potential for perianaesthetic anaphylactic reactions to NMBAs.**
- **Pharmacy and Wholesale Level Recall**
- **Date of recall: 14 March 2023.**

Background on the safety concern

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

Pholcodine-containing medicinal products have been the subject of safety reviews by the MHRA and the EU in 2011 and in 2022 regarding the potential risk that pholcodine may lead to IgE-sensitisation to NMBAs and consequently to an increased risk of anaphylactic reactions.

The 2011 review concluded that the benefit-risk balance of pholcodine-containing medicinal products in the treatment of non-productive cough was positive under normal conditions of use. However, it was concluded that the possibility of an association between pholcodine use and a perianaesthetic anaphylactic reaction to NMBAs should be further investigated. Therefore, a post-authorisation safety study (PASS) was imposed.

In 2022, the final results of the PASS, called ALPHO, became available showing a link between use of pholcodine within 12 months preceding anaesthesia with NMBAs and an increased risk of perianesthetic anaphylactic reactions related to NMBAs (odds ratio [OR] adjusted=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[1] suggest that the increased risk may persist for up to 3 years. The MHRA assessed the final results of the ALPHO study, together with additional data from available medical literature and post-marketing experience as well as independent advice from the Commission on Human Medicines (CHM).

The MHRA concluded that as it is not possible to identify who may be affected, the risk cannot be effectively mitigated and pholcodine products have therefore been withdrawn from the market as a precaution. The MAHs for pholcodine-containing medicinal products have voluntarily recalled all stock in pharmacies of the above products as a risk mitigation measure.

Advice for healthcare professionals

In case of anaesthesia requiring administration of NMBAs, anaesthetists are advised to check whether patients have used or think they may have used a pholcodine-containing medicinal product in the past, and particularly in the previous 12 months.

The Patient Information Leaflet (PIL) for pholcodine products advises patients due to undergo surgery to inform their anaesthetist if they have taken pholcodine in the past. There is an increased risk of the very rare event of an anaphylactic reaction to NMBAs when a person has taken pholcodine-containing medicinal products.

Patients should be screened on prior use of pholcodine and maintain increased vigilance in cases of confirmed exposure, particularly in the 12 months preceding surgery. Consider:

- **that it is not always possible to positively confirm past use of pholcodine (possibly due to difficulty recalling what type of medicine a patient has taken).**
- **pholcodine is not the only risk factor for NMBA anaphylaxis and anaesthetists should maintain awareness of potential perianaesthetic anaphylactic reactions to NMBAs.**

Advice to provide to patients

- Following a careful review of the evidence, including independent advice from the Commission on Human Medicines (CHM), the MHRA, which is the regulator for

[1] 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

medicines in the UK, has advised that there is an increased risk of the very rare event of an allergic (anaphylactic) reaction when:

i. a person has taken pholcodine-containing medicinal products before surgery, particularly in the past the 12 months;

ii. *and,* where neuromuscular blocking agents (NMBAs) were used to relax the muscles during surgical procedures involving general anaesthesia.

- Based on the available data, there is no immediate risk to patients who have been taking this medication, but a person receiving an NMBA during surgery under general anesthetic is at an increased risk of the very rare event of an anaphylactic reaction, if they have taken a pholcodine-containing medicine, particularly if it was in the past year.
- We advise consumers to talk to their doctor if they require general anesthesia and have taken pholcodine, particularly in the past 12 months. Your healthcare professional will be able to answer any questions you may have.
- 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, you can talk to your pharmacist who will be able to answer any questions on the most appropriate treatment for your cold and flu symptoms and suggest a suitable alternative.

Further Information

Recipients of this communication should bring it to the attention of relevant contacts by copy of this notice.

The MHRA review took place alongside a review conducted by the European Medicines Agency (EMA), which also concluded that the benefits did not outweigh the risks and that the pholcodine licences should be withdrawn from the EU market.

If you have any queries about the products being recalled, please contact the relevant company via the details in the table.

Reporting of suspected side effects

Please report suspected adverse drug reactions (ADRs) to the MHRA through the Yellow Card scheme.

You can report via:

- the Yellow Card website https://yellowcard.mhra.gov.uk/ the free Yellow Card app available from the Apple App Store or Google Play Store
- some clinical IT systems (EMIS/SystmOne/Vision/MiDatabank) for healthcare professionals

Alternatively, you can report a suspected side effect to the Yellow Card scheme by calling 0800 731 6789 for free, Monday to Friday between 9am and 5pm. You can leave a message outside of these hours.

When reporting please provide as much information as possible. By reporting side effects, you can help provide more information on the safety of this medicine.

Yours sincerely,

Michelle Riddalls
Chief Executive Officer of PAGB

Appendix I.

Product / Company & Contact	Product Licence
The Boots Company PLC Contact: Boots Customer Care Tel: 0345 0708090	
Boots Night Cough Relief Oral Solution	**PL 00014/0230**
Boots Dry Cough Syrup 6 Years+	**PL 00014/0523**
Boots Day Cold & Flu Relief Oral Solution	**PL 00014/0565**
Thornton & Ross Limited / LCM Ltd Contact: email: thorntonross@medinformation.co.uk Tel: +44 (0)1484 848164	
Cofsed Linctus	**PL 00240/0097**
Care Pholcodine 5mg/5ml Oral Solution Sugar Free	**PL 00240/0101**
Galenphol Linctus	**PL 00240/0101**
Galenphol Paediatric Linctus	**PL 00240/0102**
Galenphol Strong Linctus	**PL 00240/0103**
Covonia Dry Cough Sugar Free Formula	**PL 00240/0353**
Pholcodine Linctus (LCM Ltd)	**PL 12965/0030**
Bell Sons & Company (Druggists) Limited Contact: Mr. Trevor Price, email: trevor.price@bells-healthcare.com Tel: 0151 422 1216 / 07739 327 095	
Pholcodine Linctus Bells Healthcare 5mg Per 5ml Oral Solution	**PL 03105/0059**
Numark Pholcodine 5mg per 5ml Oral Solution	**PL 03105/0059**
Well Pharmaceuticals Pholcodine 5mg per 5ml Oral Solution	**PL 03105/0059**
Superdrug Pholcodine Linctus BP	**PL 03105/0059**
Strong Pholcodine Linctus BP	**PL 03105/0060**
Pinewood Laboratories Limited Contact: Drug Safety & Information department, Wockhardt UK Limited) Tel: 01978 661261 email: drug.safety@wockhardt.co.uk	
Pholcodine Linctus BP	**PL 04917/0002**
Strong Pholcodine Linctus BP	**PL 04917/0005**
Glaxosmithkline Consumer Healthcare (UK) Trading Limited Contact: Haleon Consumer Services: Tel: 0800 783 8881 or by email mystory.gb@haleon.com	
Day & Night Nurse Capsules	**PL 44673/0068**
Day Nurse Capsules	**PL 44673/0069**
Day Nurse	**PL 44673/0075**