<Date>

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

Dear Healthcare professional,

<Name of marketing authorisation holder> in agreement with the European Medicines Agency and the <National Competent Authority> would like to inform you of the following:

Summary

- **Use of pholcodine within 12 months preceding anaesthesia with neuromuscular blocking agents (NMBAs) has been linked to a risk of perianesthetic anaphylactic reaction to NMBAs.**
- **No effective measures have been identified to minimise this risk in patients exposed to pholcodine-containing medicinal products.**
- **As a consequence, pholcodine-containing medicinal products are being withdrawn from the European Union market.**
- **Doctors should re-evaluate their patients, consider other treatment alternatives, and advise patients to stop using pholcodine-containing medicinal products.**
- **In case of anaesthesia requiring administration of NMBAs, healthcare professionals should check whether patients have used pholcodine-containing medicinal products in the last 12 months and if so, maintain awareness of potential perianaesthetic anaphylactic reactions to NMBAs.**
- **<Recall information, if applicable, including level (pharmacy) and date of recall>.**

Background on the safety concern

Pholcodine is an opioid medicine that is used for the treatment of non-productive (dry) cough in children and adults.

Pholcodine-containing medicinal products have been the subject of two EU safety reviews in 2011 and now in 2022 regarding the potential risk that pholcodine may lead to IgE-sensitisation to neuromuscular blocking agents (NMBAs) and to anaphylactic reactions as a result.

In 2011, the safety 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 a risk of perianesthetic anaphylactic reaction related to NMBAs (OR adjusted=4.2 CI 95% [2.5; 6.9]). Data about the risk related to the use of pholcodine beyond the period of 12 months was not available. In December 2022, EMA's Pharmacovigilance Risk Assessment Committee (PRAC) assessed the final results of the ALPHO study together with additional data, including data from available medical literature and post-marketing

experience. The PRAC could not identify effective measures to minimise the risk for the patients, nor identify a patient population for whom the benefits of pholcodine-containing medicinal products could outweigh its risks. Therefore, marketing of these medicinal products will be stopped, and therapeutic alternatives should be selected. Additionally, patients should be advised to stop treatment with pholcodine-containing medicinal products. In case of anaesthesia requiring administration of NMBAs, healthcare professionals are advised to check whether patients have used pholcodine-containing medicinal products in the last 12 months and if so, maintain awareness of potential perianaesthetic anaphylactic reactions to NMBAs.

Call for reporting

<A reminder of the need and how to report adverse reactions in accordance with the national spontaneous reporting system, including the details (e.g., name, postal address, fax number, website address) on how to access the national spontaneous reporting system.>

Company contact point

<Contact point details for access to further information, including relevant website address(es), telephone numbers and a postal address.>

Communication plan

DHPC COMMUNICATION PLAN	
Medicinal product(s)/active substance(s)	Pholcodine-containing medicinal products
Marketing authorisation holder(s)	All concerned marketing authorisation holders of pholcodine-containing medicinal products. All concerned marketing authorisation holders in each Member State are strongly encouraged to collaborate, so that a single DHPC is prepared and circulated in each Member State. The letter circulated in each Member State should cover all active substance-containing products authorised in that Member State. It is encouraged that the originator marketing authorisation holder (where available) in each Member State acts as the contact point for the national competent authority, on behalf of the other concerned marketing authorisation holders in the same Member State. If no originator product is marketed in the Member State, it is encouraged that one of the concerned generic companies acts as contact point for the competent authority.
Safety concern and purpose of the communication	To inform healthcare professionals about the revocation of marketing authorisations of pholcodine-containing medicinal products.
DHPC recipients	GPs, paediatricians, pharmacists, anaesthesiologists, pulmonologists, clinical immunologists, and any other relevant target groups as agreed at national level
Member States where the DHPC will be distributed	All EU member states where pholcodine-containing medicinal products are authorised.

Timetable	Date
DHPC and communication plan (in English) agreed by PRAC	01 Dec 2022
DHPC and communication plan (in English) agreed by CMDh	14 Dec 2022
Submission of translated DHPCs to the national competent authorities for review	EC decision + 5 calendar days
Agreement of translations by national competent authorities	EC decision + 10 calendar days
Dissemination of DHPC	EC decision + 15 days