



EUROPEAN MEDICINES AGENCY  
SCIENCE MEDICINES HEALTH

01 September 2022  
EMA/PRAC/704708/2022

## PRAC List of questions

To be addressed by the marketing authorisation holder(s) for pholcodine-containing medicinal products

Article 107i of Directive 2001/83/EC

Procedure number: EMEA/H/A-107i/1521

INN/active substance: pholcodine

---

**Official address** Domenico Scarlattilaan 6 • 1083 HS Amsterdam • The Netherlands

**Address for visits and deliveries** Refer to [www.ema.europa.eu/how-to-find-us](http://www.ema.europa.eu/how-to-find-us)

**Send us a question** Go to [www.ema.europa.eu/contact](http://www.ema.europa.eu/contact) **Telephone** +31 (0)88 781 6000

An agency of the European Union



# 1. Questions

The marketing authorisation holders (MAHs) are requested to address the following questions:

## Question 1

Concerning your pholcodine-containing medicinal product(s), please provide in the annexed table:

- a) Information on type of marketing authorisation (legal basis), marketing and legal status and approved indication(s) per EU member state (MS).
- b) Patient exposure in each EU MS by product. Patient exposure should be expressed in number of patients and patient-treatment-years per product. Please indicate your method of calculation specifying the assumptions made for dose and duration of treatment.
- c) Information included in the summary of product characteristics (SmPC) and package leaflet (PL) regarding the risk for cross-sensitisation to neuromuscular blocking agents (NMBAs), and subsequent development of anaphylaxis with pholcodine-containing medicinal product(s). Please highlight the main differences between the product information (PI) of your product in the different EU MSs, as applicable.

## Question 2

The MAHs should provide:

- a) A cumulative review of all Individual Case Safety Reports (ICSRs) reporting MedDRA Preferred Terms (PTs) within the SMQ Anaphylactic reaction, where pholcodine-containing medicinal product(s) is a suspected or interacting medicinal product with relation to NMBA. The search should not be limited only to reaction field (e.g. appropriate SMQ); instead, each MAH should according to its technical possibilities search in additional fields such as case narratives, relevant medical history, relevant past drug history, etc. Cases with possible cross-sensitisation to NMBAs with pholcodine should be analysed in detail. Whenever possible, EudraVigilance case numbers for case reports should be provided and used throughout the response document. These analyses should include analyses on age and sex of patient, indication of use, duration and dose, time to onset, outcome, seriousness, concomitant medications and illnesses, relevant medical history or any other factors, such as obesity.
- b) A review and critical discussion of all available safety data relevant for the risk for cross-sensitisation to NMBAs, and subsequent development of anaphylaxis with pholcodine-containing medicinal product(s). This should include non-clinical, clinical trial data (including both MAH sponsored and non-sponsored studies), pharmaco-epidemiological studies (including observational studies), and published literature.

Particularly for the ALPHO study, the MAHs should provide all available data as appropriate and discuss the available results including their impact on the safety profile of pholcodine-containing medicinal products.

## Question 3

The MAHs are requested to discuss the possible mechanism and risk factors for cross-sensitisation to NMBAs, and subsequent development of anaphylaxis over time including a discussion on the persistence of the risk in past users, with pholcodine-containing medicinal product(s).

#### Question 4

The MAHs should provide details of any specific measures that have already been taken in order to minimise the risk for cross-sensitisation to NMBAAs, and subsequent development of anaphylaxis with pholcodine-containing medicinal product(s) and comment on the impact of such measures.

#### Question 5

The MAHs should provide a full benefit-risk balance assessment of pholcodine-containing medicinal products, taking into account impact of the safety issue on the currently approved indication(s) in the EU.

#### Question 6

The MAHs should provide proposals and justifications for any risk minimisation measures (including changes to the SmPC/PL) which may improve the benefit-risk balance of pholcodine-containing medicinal product(s). For each proposed RMM, the MAHs should discuss their feasibility and how their effectiveness should be monitored.

## Annex

### Question 1

a) & b)

<b>INN</b>	<b>Product name</b>	<b>Type of marketing authorisation (legal basis)</b>	<b>Marketing and legal status</b>	<b>Indications<sup>1</sup></b>	<b>Pharmaceutical forms and strengths</b>	<b>Sales figures</b>	<b>Estimated patient exposure<sup>2</sup></b>	<b>Doses (in clinical practice)</b>	<b>Treatment duration (in clinical practice)</b>

<sup>1</sup>. MAH should clearly indicate for which country a specifically dedicated presentation has been granted for a particular indication

<sup>2</sup>. Expressed in patient years and stratified by Member State, by indication and by age (<12, 12-18, and >18). Reasonable efforts should be made to obtain this information; potential sources in addition to sales data include registries and healthcare databases. If no precise data is available an estimate can be provided.

c)

<b>PI section</b>	<b>SmPC</b>	<b>PL</b>	<b>Main differences in SmPCs/PLs between the different EU Member States</b>