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Agence nationale de sécurité du médicament
et des produits de santé



**RATIONALE FOR THE TRIGGERING OF
PROCEDURE UNDER ARTICLE 107I OF
DIRECTIVE 2001/83/EC
ON PHOLCODINE**

AUGUST 2022

DISCLAIMER:

This assessment report was provided by the French Competent Authority (ANSM - French National Agency for Medicines and Health Products Safety) at the time of the initiation of the procedure. It provides background scientific information which complements the final notification request sent by the ANSM for an EU review.

It should be understood that this assessment report reflects the position of the French Competent Authority at the time of the initiation of the referral procedure and is without prejudice to any future position to be established on the matter by the European Medicines Agency through its Scientific Committees.

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ABBREVIATIONS

ANSM	Agence nationale de sécurité du médicament et des produits de santé (French National Agency for Medicines and Health Products Safety)
CHMP	Committee for Medicinal Products for Human Use
95% CI	95% confidence interval
CMDh	Co-ordination group for Mutual recognition and Decentralised procedures – human
IGE	Immunoglobulin-E
NMBA	Neuromuscular blocking agents
OR	Odds Ratio
PASS	Post Authorisation Safety Study
PRAC	Pharmacovigilance Risk Assessment Committee

Background

Pholcodine (3-morpholinoethylmorphine), a semi-synthetic alkaloid, is a cough suppressant that acts primarily on the central nervous system causing depression of the cough reflex, partly by a direct effect on the cough centre in the medulla. It is used alone and in combination with other active substances (e.g. bicalotymol, chlorphenamine maleate) in preparations to treat the symptoms of common cold.

In 2011, an article 31 referral was initiated by the French National Agency for Medicines and Health Products (ANSM). The Committee for Medicinal Products for Human Use (CHMP) was requested to give its opinion on whether the marketing authorisations for pholcodine-containing medicinal products should be maintained, varied, suspended or withdrawn. The concerns arose from the potential risk that pholcodine may lead to IgE-sensitisation to neuromuscular blocking agents (NMBAs). The hypothesis of the role of pholcodine, raised in 2005 by the Norwegian team of E. Florvaag and the Swedish team of S.G.O. Johansson, was mainly based on specific IgE tests, without information on the confirmation of anaphylactic reactions by skin tests with NMBAs, nor cutaneous explorations of hypersensitivity to pholcodine. In 2007, six years after the withdrawal of pholcodine in Norway, these teams confirmed a decrease in sensitization to NMBAs in the general Norwegian population. After a thorough review of the available data as part of the referral procedure, the CHMP established that the evidence of a link between pholcodine and NMBA-related anaphylaxis was circumstantial, not entirely consistent and did not support the conclusion that there was a significant risk of cross-sensitisation to NMBAs and subsequent development of anaphylaxis during surgery. The CHMP therefore concluded that, based on currently available information, the benefit-risk balance of pholcodine-containing products in the treatment of non-productive cough was positive under normal conditions of use and recommended the maintenance of the marketing authorisations. However, the CHMP also concluded that further investigation on the possibility of an association between pholcodine use and NMBA-related anaphylaxis was needed. As an outcome of this referral the conduct of a PASS (post-authorisation safety study) was imposed as a condition of the marketing authorisations of pholcodine-containing products.

Enrolment started in 2014 and finished in July 2020 but the results were not available in 2021 due to accumulated delays including slow recruitment rates over the years and later the coronavirus disease (COVID-19) pandemic.

Meanwhile, in 2021, an Australian team (Sadleir et al, 2021) published the results of a monocentric study conducted in Western Australia that compared a group of patients with anaphylaxis to NMBAs (i.e. rocuronium and vecuronium) to a group of patients who had anaphylaxis to cefazolin with respect to BMI grade, history of pholcodine consumption, sex, age, comorbid disease, and NMBA type and dose. Patients were included prospectively and retrospectively, and collection of data of pholcodine consumption were carried out retrospectively, several years earlier for some patients leading to a potential increased risk of memory bias. The results highlighted the role of obesity as a risk factor for NMBA anaphylaxis and showed that pholcodine consumption was associated with a very significant risk of anaphylaxis to NMBA muscle relaxants (adjusted OR =12.7, 95% CI [3.8 – 43.1], $p < 0.001$). Considering only concurrent cases to decrease the likelihood of bias due to pholcodine exposure misclassification, pholcodine consumption was observed in 56.6% of cases and in only 36.4% of controls but remained a significant risk factor (OR=2.28, $p=0.042$). This was the first time pholcodine consumption has been shown to be a risk factor of NMBA anaphylaxis in a clinical study. This study was assessed during the Periodic Safety Update Report single assessment (PSUSA) procedure of pholcodine in 2022 (PSUSA/00002396/202105). As an outcome, notwithstanding the different anaesthesia practices and thus the fact that the results from the Australian study cannot be fully extrapolated to the EU, the PRAC considered that a causal relationship between pholcodine and cross-reactivity to NMBAs could not be ruled out and recommended to update the product information of all pholcodine-containing products (including fixed dose combinations), while waiting for the results

of the ALPHO study, to warn patients and healthcare professionals that cross-reactivity leading to serious allergic reactions (anaphylaxis) have been reported between pholcodine and NMBA. The Co-ordination Group for Mutual Recognition and Decentralised procedures - Human (CMDh) agreed on this variation of the marketing authorisations based on the PRAC recommendation and in addition, requested the MAHs involved in the ALPHO study to provide results of the study as soon as possible and no later than 30th of June 2022 (CMDh meetings on 25-27 January 2022 and on 21-22 June 2022).

Safety (new data)

On 30th June 2022, the ANSM received a preliminary study report of the PASS ALPHO from the sponsor (Nancy University hospital) providing the results of the analysis on the primary endpoint. No further analyses for primary endpoint are expected to be presented in the final report.

The primary objective of this case-control study was to investigate an association between pholcodine exposure and the risk of perianaesthetic NMBA-related anaphylactic reaction by comparing a group of patients who experienced a anaphylactic reaction at anaesthetic induction to a group of patients anaesthetized with NMBA injection who did not experience a perianaesthetic anaphylactic reaction (control patients) matched (ratio 2:1) on age, gender, NMBA category, time of anaesthesia, and geographic region.

The study included a total of 937 patients for 167 cases and 334 controls. The results on the primary endpoint of the study showed a statistically significant link between exposure to pholcodine during the 12 months preceding surgery and a risk of perianaesthetic anaphylactic reaction related to NMBA after adjusting for potential confounding factors (adjusted OR = 4.4, 95% CI [2.6; 7.3] $p < 10^{-4}$). These data on the preliminary outcome are consistent with the Australian study from Sadleir et al and support the pholcodine hypothesis.

The ALPHO study was imposed after the 2011 referral specifically to investigate the possibility of an association between pholcodine use and NMBA-related anaphylactic and provides more robust results for the EU than the Australian study as per the methodology (multicentric study conducted in the EU in a significant number of patients).

Incoming data from analyses of the secondary objectives and based on skin tests with pholcodine solution and total and specific IgE assays could help to clarify the mechanisms involved, but are not expected to have an impact on the preliminary results that already confirm the hypothesis of an association between exposure to pholcodine and an increased risk of perianaesthetic anaphylactic reaction. In addition, it should be highlighted that this risk can be life-threatening and also appears to be unpredictable especially when NMBA are used in an emergency situation considering this risk persists for several months after exposure to pholcodine.

Considering the importance of the risk that is evidenced from ALPHO, the fact that these results concur with the results of the Australian study, and considering the symptomatic indication, the ANSM considers that measures to protect the population should be taken without delays.

Efficacy

Efficacy data of pholcodine containing products were reviewed during article 31 referral in 2011, no new significant efficacy data are available since then. Efficacy data on pholcodine are based on a large body of literature demonstrating the existence of centrally-acting cough suppressant properties of opiates, and pholcodine in particular has been used in this indication since the 1950's. Being such an

old product, the methodology used in most efficacy studies with pholcodine would be considered poor by modern standards. Most studies were not adequately controlled, either with active or placebo medications, and some were performed using combination products, which makes it difficult to isolate and measure the efficacy of the single component pholcodine. No study has been performed on the long-term effects of pholcodine, with the majority of trials ranging from a few days to one week duration. Nevertheless, the existing data are consistent and supportive of the efficacy of pholcodine in the treatment of acute non-productive cough. The most recent study conducted by Zambon Equinozzi R et al, (2006), comparing pholcodine and dextrometorphan in a randomised and blinded design, showed they had similar efficacy in reducing day and night-time cough frequencies in adult patients suffering with acute non-productive cough. This study had limitations such as a lack of a placebo control arm and the non-validated and subjective nature of the outcomes (cough frequency and intensity measured by cough scores on a 5-point scale recorded at home on a diary card by the patients on each day of treatment), but an effect was observed very early in the treatment.

Overall and regardless of effectiveness in its current approved indication, pholcodine is used to treat non-life threatening functional symptoms diseases with spontaneous resolution without treatment.

Benefit-risk evaluation and recommendations

The benefit of pholcodine in the symptomatic treatment of cough is moderate and the risk of anaphylactic reaction could be life-threatening, unpredictable in an emergency situation and is persistent for at least several months after exposure. Taking into account that pholcodine is used to treat non-life threatening functional symptoms diseases with spontaneous resolution, the ANSM considers that the benefit-risk ratio of this product is no longer considered favourable. In light of the above, the ANSM considers that marketing authorisation of all pholcodine-containing products including fixed-dose combinations, should be suspended in France, and an urgent Union procedure under Article 107i of Directive 2001/83/EC should be initiated.

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