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Pharmacovigilance Risk Assessment Committee (PRAC)

Assessment report

Procedure under Article 107i of Directive 2001/83/EC

Pholcodine-containing medicinal products

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

Note:

Assessment report as adopted by the PRAC and considered by the CMDh with all information of a commercially confidential nature deleted.

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1. Information on the procedure

The results of the ALPHO study showed a statistically significant link between exposure to pholcodine and the risk of perianaesthetic anaphylactic reaction related to neuromuscular blocking agents (NMBAs). ALPHO study was an imposed post-authorisation safety study (PASS) assessing the risk of anaphylaxis to NMBAs after use of pholcodine conducted as a condition of the marketing authorisations of pholcodine-containing medicinal products following a previous referral in 2011. In light of the new data from this PASS, taking into account the seriousness and the unpredictability of this risk and that pholcodine-containing medicinal products are used to treat non-life-threatening functional symptoms (non-productive cough), the French medicines agency (ANSM) was of the view that the benefit-risk ratio of pholcodine-containing medicinal products was no longer favourable and considered suspending the marketing authorisations of these products in France.

On 19 August 2022, ANSM therefore triggered an urgent Union procedure under Article 107i of Directive 2001/83/EC and requested the PRAC to assess the impact of the above concerns on the benefit-risk balance of pholcodine-containing medicinal products and to issue a recommendation on whether the relevant marketing authorisations should be maintained, varied, suspended or revoked.

2. Scientific discussion

2.1. Introduction

Pholcodine is a morphinane alkaloid that is a derivative of morphine with a 2-morpholinoethyl group at the 3-position. It is an opiate acting directly on the medulla oblongata, cough centre of the central nervous system (CNS) used for treatment of cough and cold symptoms in children and adults.

Pholcodine has been used as a cough suppressant since the 1950s. In the European Union (EU), pholcodine-containing medicines are currently approved in seven EU Member states (MSs): Belgium, Croatia, France, Ireland, Lithuania, Luxembourg and Slovenia. Pholcodine-containing products are also available in Northern Ireland. Pholcodine-containing products are marketed in the EU MSs for symptomatic treatment of acute dry, non-productive cough in adults and children. Age limit for use in children varies between the authorised products with 30 months being the lowest age limit authorised. Pholcodine-containing medicinal products are available both with and without medical prescription. The products available without medical prescription have limited duration of use up to several days after which medical advice should be sought which is in line with general guidance for over-the-counter (OTC) products. A rough estimate of the cumulative exposure for all products in all EU countries combined is approximately 1 025 437 089 patient-years. The exposure is the highest in France, where the cumulative exposure is approximately 1 022 141 456 patient-years.

In 2011, an article 31 referral was initiated by the ANSM concerning a potential risk of IgE-sensitisation to NMBAs, such as atracurium, cisatracurium, mivacurium, pancuronium, rocuronium, suxamethonium and vecuronium, with pholcodine use. The referral was triggered following the publication of literature data suggesting a link between pholcodine consumption and cross sensitization to NMBAs resulting in anaphylactic reactions during anaesthesia. The published data referred mainly to Norway and Sweden, where pholcodine was no longer marketed. In France, data from spontaneous reporting suggested a 25% increase in the number of anaphylactic shocks to NMBAs in the period 2008/2009 when compared to the 2003/2004 period. This coincided with a 9% increase in the consumption of pholcodine-containing products in France between the two periods. As a consequence, ANSM changed the prescription status of pholcodine-containing medicines to prescription only and triggered an article 31 referral.

After a thorough review of available data during the referral procedure in 2011, the Committee for Medicinal Products for Human Use (CHMP) established that the evidence of a link between pholcodine use and NMBA-related anaphylaxis was circumstantial, not entirely consistent and not supportive of a conclusion that there was a significant risk of cross-sensitisation to NMBAs and subsequent development of anaphylaxis during surgery. 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.

Meanwhile, in 2021, an Australian team (Sadleir, 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. 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. This study was assessed during the Periodic Safety Update Report single assessment (PSUSA) procedure of pholcodine finalised in 2022 (PSUSA/00002396/202105). As an outcome, notwithstanding the different anaesthesia practices and thus the fact that the results from the Australian study could not 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, while waiting for the results of the ALPHO study, to update the product information of all pholcodine-containing products (including fixed dose combinations) to warn patients and healthcare professionals (HCPs) that cross-reactivity leading to serious allergic reactions (anaphylaxis) have been reported between pholcodine and NMBAs.

The preliminary results of the ALPHO study, the imposed post-authorisation safety study (PASS) assessing the risk of anaphylaxis to NMBAs after use of pholcodine conducted as a condition of the marketing authorisations of pholcodine-containing medicinal products following the previous referral in 2011 were received by ANSM on 30 June 2022. The study results showed a statistically significant link between exposure to pholcodine and the risk of perianaesthetic anaphylactic reaction related to NMBAs.

Based on these new data which are consistent with the Australian study from Sadleir et al, the ANSM considered the hypothesis that pholcodine consumption is likely associated with a risk of unpredictable perianaesthetic NMBA-related anaphylactic reaction, as confirmed. Even if the Australian study has shown that pholcodine consumption could be a risk factor of NMBA anaphylaxis, the results of this monocentric study could not be fully extrapolated to the EU due to different anaesthesia practices. The ALPHO study was imposed after the 2011 referral as a condition of the marketing authorisation for the EU, and provided more robust results as per the methodology (multicentric study conducted in the EU in a significant number of patients).

In light of the new data from the PASS, taking into account the seriousness and the unpredictability of this risk and that pholcodine-containing medicinal products is used to treat non-life-threatening functional symptoms (non-productive cough), the ANSM was of the view that the benefit-risk ratio of pholcodine-containing medicinal products was no longer favourable and considered suspending the marketing authorisations of these products in France.

After the start of the urgent Union procedure under Article 107i, pholcodine-containing products have been suspended in three EU MSs: France, Belgium and Luxembourg. Additionally, the final study results were received by ANSM on 15 September 2022.

The PRAC considered all available data, including the results of observational studies (including the ALPHO study), literature data, post-marketing case reports as well as responses submitted by the

MAHs and the submissions by the stakeholders. A summary of the most relevant information is included below.

2.2. Data on the risk of anaphylaxis to NMBAs

2.2.1. PASS results (ALPHO)

The post-marketing case-control ALPHO study[1] was conducted in France (24 centers) as per the recommendation of the CHMP by collaboration of fourteen MAHs. Enrolment started in 2014 and finished in July 2020 but the results were not available in 2021 due to some accumulated delays including slow recruitment rates over the years and later the coronavirus disease pandemic (COVID-19). The results were received by ANSM in 2022.

Methods

The primary objective of the ALPHO study was to investigate an association between pholcodine exposure and the risk of perianaesthetic anaphylactic reaction related with NMBA by comparing a group of patients who experienced a anaphylactic reaction at anaesthetic induction (case patients) 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 secondary objectives of the study were:

- to compare anti-pholcodine IgE, anti-ammonium IV IgE and total IgE levels between the case and control groups;
- to study the correlation between exposure to pholcodine in cases and controls, by means of a patient self-questionnaire on the one hand and, on the other hand, by a computerized drug history, supplemented by pharmaceutical file, if applicable;
- to study the impact of taking 1, 2 or 3 information sources in order to estimate pholcodine exposure;
- to study the association between exposure to pholcodine and the presence/levels of pholcodine-specific IgE, reflecting sensitisation to pholcodine;
- to study NMBA and pholcodine cross-sensitisation by testing skin reactions to pholcodine in case patients allergic to (at least) one NMBA;
- to compile a biological collection to study the predictive risk factors associated with immediate allergies.

The following inclusion criteria was followed for case and control patients:

Case Patients:

- Man or woman, ≥ 2 years old.
- Went to an allergy-anaesthesia consultation between 6 to 12 weeks (approximately) following the occurrence of a perianaesthetic anaphylactic reaction during the introduction of anaesthesia with the administration of NMBA(s).
- Given their consent (consent from both parents for a minor child).
- Affiliated to social security regime or beneficiary.

[1] https://clinicaltrials.gov/ct2/show/NCT02250729, accessed on 11/10/2022

- Able to answer a questionnaire regarding medication history.
- Having a clinical state compatible with carrying out skin tests (absence of a dermatological or psychiatric illness, etc.).
- Stopped any anti-histamine treatment for at least 8 days.

Control Patients:

- Man or woman, ≥ 2 years old.
- Patient anesthetized in a control recruitment centre.
- Having undergone anaesthesia with an NMBA injection without the occurrence of a perianaesthetic anaphylactic reaction, regardless of their medical background.
- Given their consent (consent from both parents for a minor child).
- Affiliated to a social security regime or beneficiary.
- Able to answer a questionnaire regarding medication history.

Pholcodine exposure in the 12 months prior to anaesthesia was measured through a self-reported questionnaire, patient's medical history and patient's electronic pharmaceutical file.

Results

The study included a total of 937 patients for 167 cases and 334 controls. Women represented 55.1% of the matched population. This is in line with the available French data that indicates that allergy to NMBAs is more common in women than men, with three of four reactions occurring in females (Mertes, 2011). The mean age was 56 years old (SD=13.1) in cases and the mean age was 57 years old (SD=15.7) in controls. This is also in line with data indicating that perioperative anaphylaxis occurs in children less frequently than in adults (Wakimoto, 2021). The mean BMI was 27.4 (SD=8.2) in cases and 27.4 (SD=7.3) in controls. Regarding pholcodine exposure, 79 (47.3%) cases and 67 (20.1%) controls had been exposed to pholcodine within 12 months before inclusion. No case or control had a known allergy to pholcodine. Of note, 33 (19.8%) cases and 18 (5.4%) of controls reported a current or previous occupation exposed to quaternary ammoniums (hairdressing or cleaning/maintenance). In addition, 150 (89.8%) cases and 309 (92.5%) controls had already undergone surgery before inclusion.

The primary results showed a statistically significant link between use of pholcodine during the 12 months preceding anaesthesia and risk of perianaesthetic anaphylactic reaction related to NMBAs (OR adjusted=4.2 CI 95% [2.5; 6.9][2]). Professional exposure to quaternary ammoniums ($p<10^{-4}$) and history of hepatogastrointestinal disorders (p=0.004) were also associated with the risk of a perianaesthetic anaphylactic reaction related to a NMBA.

The study analysed the concentrations of IgE anti-pholcodine, IgE anti-quaternary ammoniums and total IgE of cases and controls. An increase of pholcodine IgE and total IgE was hypothesized after pholcodine exposure, but this hypothesis was not verified in study population, possibly because of small number of patients, subgroup analysis and thus lack of statistical power, meaning that IgE levels obtained in this study cannot be used to predict an allergy reaction to NMBA. Specific IgE antibodies to quaternary ammonium and pholcodine showed a good performance to discriminate case patients from controls. Specific IgE antibodies to quaternary ammonium and pholcodine results provided a good negative predictive value to reasonably rule out NMBA anaphylactic risk when specific IgE antibodies

[2] The OR value calculated and presented in preliminary study result and in the notification of the procedure under Article 107i is different from the final result presented in this report.

are undetectable. Conversely, the positive predictive value was very low, meaning that the presence of specific IgE could not allow to identify a population at risk with sufficient precision. Significant correlations were seen between pholcodine and quaternary ammonium IgE.

Most patients who have experienced an anaphylactic shock to NMBAs had positive skin tests for pholcodine, but there was no difference in these results between the exposed and unexposed to pholcodine. The study authors reported that this may indicate either that Pholcodine is irritating or that there is frequent cross-reactivity with NMBAs.

2.2.2. Literature

Literature was screened to identify available evidence about pholcodine and risk of NMBA cross-reactivity. Several publications can be found on the topic of pholcodine hypothesis, including discussion about the mechanism, influence of other substances with quaternary ammonium ions found in household products or to which certain professions such as hairdressers and cleaners are exposed to and description of the effect of pholcodine withdrawal from the Norwegian market.

Description of individual studies

1. Florvaag et al, 2005

In 2005, Florvaag et al. studied 300 sera of 'allergies' and 500 blood donors in Bergen and Stockholm, which were tested for IgE antibodies to morphine and suxamethonium and the results were compared to those of 65 patients from Bergen with documented anaphylaxis to NMBA. In addition, 84 different household chemicals were tested, by IgE antibody inhibition, for suxamethonium and morphine. The authors reported that IgE-sensitization to suxamethonium, morphine and pholcodine was detected in Norway but not in Sweden. Of the anaphylactic, 65-68% were sensitized to morphine or pholcodine but only 39% to suxamethonium. The authors indicated that a possible explanation was the unrestricted use of cough mixtures containing morphine derivatives in Norway.

2. Florvaag et al, 2006

In 2006, Florvaag et al. conducted a pilot study to explore the effect of exposure to cough syrup and environmental chemicals containing pholcodine, morphine and suxamethonium related allergenic structures on IgE production in IgE-sensitized and non-sensitized individuals. Serum concentrations of IgE and IgE antibodies to pholcodine, morphine and suxamethonium allergens were followed after intake of cough syrup, or exposure to confectionary and other household chemicals containing various amounts of substances cross-reacting with pholcodine, morphine and suxamethonium. The results indicated that cough syrup containing pholcodine gave, in sensitized individuals, within 1-2 weeks, an increase of IgE of 60-105 times and of IgE antibodies to pholcodine, morphine and suxamethonium in the order of 30-80 times. The tested confectionary did not have any similar stimulating effect but seemed to counteract the expected decrease of IgE. No effect was seen in nonsensitized individuals. The pholcodine stimulated IgE showed a nonspecific binding to ImmunoCAP with common allergens and glycine background ImmunoCAP that was up to 10-fold higher than that of monomeric myeloma-IgE at twice the concentration. The authors concluded cough syrups containing pholcodine have a IgE boosting effect in persons IgE-sensitized to pholcodine, morphine and suxamethonium related allergens. Household chemicals containing such allergenic epitopes seemed capable of some, minor, stimulation.

3. Harboe et al, 2007

Harboe et al. conducted a randomized controlled trial to explore the effect of pholcodine exposure on IgE in a population with previously diagnosed IgE-mediated anaphylaxis towards NMBAs. Seventeen

patients were randomized to 1 week's exposure with cough syrup containing either pholcodine or guaifenesin. The primary variables serum IgE and IgE antibodies towards pholcodine, morphine and suxamethonium were measured before and 4 and 8 weeks after start of exposure. The results showed that patients exposed to pholcodine had a sharp rise in levels of IgE antibodies towards pholcodine, morphine and suxamethonium, the median proportional increases 4 weeks after exposure reaching 39.0, 38.6 and 93.0 times that of the base levels respectively. Median proportional increase of IgE was 19.0. No changes were observed in the guaifenesin group. The authors concluded that serum levels of IgE antibodies associated with allergy towards NMBAs increase significantly in sensitized patients after exposure to cough syrup containing pholcodine.

4. Johansson et al, 2009

In 2009, Johansson et al. published a report indicating that pholcodine caused anaphylaxis in Sweden 30 years ago. Pholcodine was marketed in Sweden during the 1970s and 1980s. Stored serum samples collected from patients with an IgE-mediated allergy during the period 1970-1999 were tested for IgE antibodies to morphine, pholcodine and suxamethonium. The accumulated number of reported cases of anaphylaxis was high in the 1970s. The percentage of sera with antibodies to pholcodine and morphine dropped from the 1970s to the 1990s, although the pattern was less clear with suxamethonium. No case was reported after 1990 when pholcodine was no longer on the market. The authors concluded at the time of the publication that the pholcodine hypothesis was strengthened, and thus a general, global withdrawal of all drugs containing pholcodine needed to be seriously considered, as morbidity would be reduced and lives saved from the reduction or disappearance of anaphylaxis to NMBA.

5. Johansson et al, 2010

In 2010, Johansson et al. published results of the study that aimed to test, on a multinational level, the pholcodine hypothesis, i.e. that the consumption of pholcodine-containing cough mixtures could cause higher prevalence of IgE antibodies to pholcodine, morphine and suxamethonium. National pholcodine consumptions were derived from the United Nations International Narcotics Control Board database. IgE and IgE antibodies to pholcodine, morphine, suxamethonium and P-aminophenyl-phosphoryl choline were measured in sera from atopic individuals collected in nine countries representing high and low pholcodine-consuming nations. Results showed a significant positive association between pholcodine consumption and prevalence of IgE-sensitization to pholcodine and morphine, but not to suxamethonium and and P-aminophenyl-phosphoryl choline, as calculated both by exposure group comparisons and linear regression analysis. The Netherlands and the USA did not have pholcodine-containing drugs on the markets, although the former had a considerable pholcodine consumption. Both countries had high figures of IgE-sensitization. The authors concluded that this international prevalence study additionally supported the pholcodine hypothesis and, consequently, that continued use of medicines containing the substance would need to be questioned.

6. Chalabianloo et al, 2010 (conference abstract)

Chalabianloo et al. reported in 2010, as a conference abstract, the results of their study that aimed to describe the clinical characteristics of patients with suspected drug hypersensitivity. The medical records of 20 consecutive patients with suspected drug hypersensitivity, enrolled from a large retrospective study designed to include about 400 patients consulted in a Norwegian Allergy Centre, were investigated with respect to history, skin tests and serology. Among results, anaphylaxis was reported in 10 patients, and 45% of the reactions occurred within 1 hour after taking the drug. Total serum IgE was increased (> 120 KU/L) in 40% and serum ECP was increased (> 22.0 mug/L) in 20% of patients. 3 patients had antigen-specific IgE antibody concentration above 0.35 KU/L (2 to penicillin and 1 to morphine/pholcodine).

7. Florvaag et al, 2011

This study aimed to describe the effects of withdrawal of pholcodine on IgE, IgE-antibodies and reported frequencies of anaphylaxis to NMBAs. Three hundred sera from supposedly allergic patients sampled yearly through 2006 to 2010 were analysed for IgE antibodies to pholcodine, suxamethonium and morphine. Furthermore, IgE and preliminary reports from the Norwegian Network for Anaphylaxis under Anaesthesia were monitored. Results showed that pholcodine exposure was associated with IgE sensitization to pholcodine, morphine and suxamethonium. However, after withdrawal, within 1 year, antibody prevalence to pholcodine and suxamethonium fell significantly from 11.0% to 5.0% and from 3.7% to 0.7%, respectively. At 3 years, suxamethonium had fallen to 0.3%, pholcodine to 2.7% and morphine to 1.3%. By 2 years, the prevalence of elevated IgE was significantly reduced. After 3 years, the incidence of reported suspected anaesthetic anaphylaxis fell significantly, both the total number, the reactions related to NMBAs and those with IgE antibodies to suxamethonium. The authors concluded that withdrawing of pholcodine lowered significantly within 1-2 years levels of IgE and IgE antibodies to pholcodine, morphine and suxamethonium, and, within 3 years, the frequency of NMBA suspected anaphylaxis. The authors stated that results strengthened the pholcodine hypothesis considerably and equally the need to question the existence of cough depressants containing pholcodine.

8. Clarke et al, 2011 (conference abstract)

In a conference abstract presented in 2011, Clarke et al. presented a ten-year retrospective study of anaphylaxis caused by muscle relaxants in Western Australia. All cases of NMBA anaphylaxis between 2000 and 2010 were reviewed. The results showed there were 75 cases of anaphylaxis in the study period. At the same time, there were 1,816,437 general anaesthetics, 35 to 45% of which included a NMBA. The risk of anaphylaxis in Western Australia from a NMBA per exposure was 1/8500 to 1/10,900. During the study period, rocuronium was used on average 1.42 times more than vecuronium. Cross-reactivity was absent in 25% of cases. In one case cross-reactivity was demonstrated to all NMBA tested. Suxamethonium and rocuronium most commonly cross-reacted whereas cisatracurium did so the least. There were no deaths, but two cases were associated with residual cerebral dysfunction. The authors discussed that anaphylaxis rates to NMBA vary from 1/5200 - where pholcodine is freely available - to 1/200,000 where it is not. In Western Australia, the rate was consistent with the former. Cross-reactivity was not entirely predictable on the basis of structure. There was insufficient data to make any judgment about relative risk of allergic reactions with those neuromuscular blocking agents rarely used, but the cross-reactivity rates would support the belief that suxamethonium is particularly allergenic. When comparing the usage of rocuronium and vecuronium with their proportion of the total number of cases of neuromuscular blocking agent anaphylaxis, a relative risk index of 2.89 could be calculated. This was supported in the cross-reactivity data where rocuronium is the second most likely drug (after suxamethonium) to skin test positive. Cisatracurium was the least likely NMBA to cross-react.

9. Johansson et al, 2012 (case series)

In this article, the authors present four case reports of anaphylaxis to atracurium in Sweden, in which none was IgE sensitised to morphine, pholcodine or suxamethonium. One case had a positive basophil test (basophil allergen threshold sensitivity) to atracurium, but was negative to the other NMBAs. Serological testing showed that two of the four patients had IgE antibodies to atracurium. The IgE binding could be completely inhibited by atracurium, but not by the other six NMBAs or by pholcodine.

10. Dong et al, 2013 (exposure to professional occupational factors)

The study aimed to investigate the prevalence of specific IgE to quaternary ammonium ions in two populations professionally exposed to quaternary ammonium compounds, in the North-Eastern France.

The authors observed a 4.6-fold higher frequency of positive IgE against quaternary ammonium ions in hairdressers, compared with baker/pastry makers and control groups. The competitive inhibition of quaternary ammonium Sepharose radioimmunoassay with succinylcholine was significantly higher in hairdressers, compared with baker/pastry makers and control groups, with inhibition percentage of 66.2 +/- 7.4, 39.7 +/- 6.0 and 43.8 +/- 9.9, respectively ($P < 0.001$). The specific IgE against quaternary ammonium ions recognized also two compounds widely used by hairdressers, benzalkonium chloride and polyquaternium-10. When considering the whole study population, hairdresser professional exposure and total IgE > 100 kU/L were the two significant predictors of IgE-sensitization against quaternary ammonium ions in the multivariate analysis of a model that included age, sex, professional exposure, increased concentration of total IgE (IgE > 100 kU/L) and positive IgE against prevalent allergens ($P = 0.019$ and $P = 0.001$, respectively). As conclusion, the authors considered that the study suggested that repetitive exposure to quaternary ammonium compounds used in hairdressing is a risk factor for NMBAs sensitization.

11. Katelaris et al, 2014

Serum samples in Australia, Japan and Republic of Korea were tested for IgE antibodies to suxamethonium, pholcodine and morphine. The prevalence of IgE-antibodies to pholcodine, morphine, and suxamethonium were 10%, 8.6%, and 4.3%, respectively, in Australia. The corresponding figures for Japan were 0.8%, 0.8%, and 1.5%, and for Korea 1.0% to pholcodine and 0.5% to morphine and suxamethonium. Of the suxamethonium-positive sera, 100% were positive to pholcodine or morphine in Australia and 0% in Japan and Korea.

12. De Pater et al, 2017

The authors conducted a six-year follow-up study on the effects of pholcodine withdrawal on IgE sensitization and anaphylaxis reporting. From 650 acute consecutive reports (2005-2013) to the Norwegian Network for Anaphylaxis under Anaesthesia, total number of reports on suspected anaphylactic reactions, number of reactions where NMBAs were administered, number of reactions where serum IgE antibodies (≥0.35 kUA /l) to suxamethonium and pholcodine were present at time of reaction and anaphylaxis severity grades were retrieved. In addition, NMBA sales and prevalence of IgE sensitization to pholcodine and suxamethonium among 'allergics' were monitored. From baseline period P0 (pholcodine on the market) through the first (P1) and second (P2), three-year periods after withdrawal, significant falls in total reports ($P<0.001$) and reports with IgE antibodies to pholcodine ($P=0.008$) and suxamethonium ($P=0.001$) at time of reaction were found. Total NMBA sales in P2 were 83% of P0, and suxamethonium and rocuronium together made up 86% of sales throughout the study. Five NMBA-related anaphylactic deaths occurred during P0 and P1 and, however, none during P2. Prevalence of IgE sensitization to suxamethonium in 'allergics' fell to 0% at 4 and 5 years after withdrawal. The authors considered that the decline suggested that the Norwegian population had gradually become less IgE-sensitised and clinically more tolerant to NMBA exposure.

13. Anderson et al, 2020

The authors note that specific IgE to NMBAs is frequently examined using morphine as a marker for the substituted ammonium groups considered to be the main allergenic epitopes of NMBAs and pholcodine (a morphine derivative) has also been suggested as an effective marker for detection of specific IgE to substituted ammonium epitopes. However, considerable variation can be seen between specific IgE concentrations to morphine or pholcodine in NMBA-allergic patients. The analysis reported by the authors was undertaken to investigate these variations and the value of the pholcodine specific IgE assay in the assessment of NMBA allergic patients. A retrospective study was carried out for all patients investigated at the Royal North Shore Hospital Anaesthetic Allergy Clinic (Sydney, Australia) from June 2009 to September 2019. Standardised skin testing was performed with a panel of NMBAs

including rocuronium, vecuronium, pancuronium, succinylcholine, and cisatracurium. Measurement of pholcodine and morphine specific IgE was performed for all patients. A total of 801 consecutive patients were examined. Of these, 255 exhibited positive skin test results for NMBAs (187 female, 68 male, median age 52 years). Pholcodine specific IgE concentrations were quantitatively higher than morphine specific IgE concentrations in 56% of skin test positive patients. Where patients had pholcodine specific IgE concentrations two or more times the concentration of morphine specific IgE, a significantly increased proportion had skin sensitisation to succinylcholine. The authors concluded that comparison of variation in the concentrations of specific IgE between the pholcodine and morphine substrates may provide increased information regarding which NMBAs could present a risk for future procedures, with results from the current analysis indicating that this may be of use in the assessment of risk associated with subsequent succinylcholine exposure.

14. Sadleir et al, 2021

In this study, 145 patients diagnosed with intraoperative NMBA anaphylaxis in Western Australia between 2012 and 2020 were compared with 61 patients with cefazolin anaphylaxis with respect to BMI grade, history of pholcodine consumption, sex, age, comorbid disease, and NMBA type and dose. Confounding was assessed by stratification and binomial logistic regression. Obesity (odds ratio [OR]=2.96, $\chi2$=11.7, P=0.001), 'definite' pholcodine consumption (OR=14.0, $\chi2$=2.6, P<0.001), and female sex (OR=2.70, $\chi2$=9.61, P=0.002) were statistically significant risk factors for NMBA anaphylaxis on univariate analysis. The risk of NMBA anaphylaxis increased with BMI grade. Confounding analysis indicated that both obesity and pholcodine consumption remained important risk factors after correction for confounding, but that sex did not. The relative rate of rocuronium anaphylaxis was estimated to be 3.0 times that of vecuronium using controls as an estimate of market share, and the risk of NMBA anaphylaxis in patients presenting for bariatric surgery was 8.8 times the expected rate (74.9 vs 8.5 per 100 000 anaesthetic procedures). The authors concluded that obesity is a risk factor for NMBA anaphylaxis (the risk increasing with BMI grade), pholcodine consumption is an additional risk factor and rocuronium use is associated with an increased risk of anaphylaxis compared with vecuronium in this population.

15. Malvik et al, 2022

The authors reported that in Norway, from 1997 to 2007, there was a mean of 76 reports per year, and after an initial yearly increase in number of reports following the establishment of the registry, there was a mean of 87 yearly reports from 2001 to 2007. After 2007, the mean number of reports fell to 61, with stable reporting from 2009.

2.2.3. Post-marketing data

The MAHs have performed analysis of cases reported to their pholcodine-containing products and presented data in their responses. Cumulatively, there were a total of 88 cases identified in MAHs safety databases reporting PTs from the SMQ Anaphylactic reaction where pholcodine-containing medicinal product(s) is a suspected or interacting medicinal product with relation to NMBA. Additionally, three MAHs performed searches for similar cases in the EudraVigilance database. Provided details about cases were analysed by the PRAC to assess whether cases concern safety issue of interest (anaphylaxis to NMBAs with previous exposure to pholcodine). Cumulatively there were 24 cases from either MAHs databases or EudraVigilance. It was not possible to exclude duplicates since not all MAHs provided case numbers. 14 cases were serious, 1 was non-serious, while other 9 were missing data about seriousness. 3 cases reported fatal outcome, 7 cases reported outcome as recovered or recovering, while in other 14 cases outcome was unknown. Time between pholcodine exposure and onset of anaphylaxis ranged between 2 and 3 months in cases where it was reported.

Overall, analysed cases from either MAHs databases or EudraVigilance raise suspicion regarding association between pholcodine and anaphylaxis to NMBAs. Most of the ICSRs analysed, based on their Eudravigilance numbers where it was available, originated either from France or Australia where the two recent studies (ALPHO and Sadleir, 2021) were performed. Therefore, cases presented in the MAHs' reviews could be result either of ICSRs originating from published medical literature or due to raised awareness amongst medical professionals and therefore increased spontaneous reporting rate. It is also possible that most of these patients (and suspected ADRs) are already included in results from respective studies which are discussed in this report.

2.2.4. Discussion on the risk of anaphylaxis to NMBAs

Anaphylaxis is a serious systemic hypersensitivity reaction that is usually rapid in onset and may cause death. Severe anaphylaxis is characterized by potentially life-threatening compromise in airway, breathing and/or the circulation, and may occur without typical skin features or circulatory shock being present (Cardona, 2020). Perioperative anaphylaxis, including anaphylaxis to NMBAs, is a serious and life threatening medical condition which is rare (1/10.000 anaesthesia procedures) but with relatively high mortality (4-6%) despite immediate access to treatment in the anaesthetic department. Perioperative anaphylaxis can occur via IgE-dependent mechanism, which account for approximately 60 percent of perioperative anaphylaxis, non-IgE-dependent immunological mechanisms (mediated by IgG or IgM antibodies or by antigen-antibody complexes and complement) or nonimmunologic mechanisms involving direct release of histamine and other mediators from mast cells and basophils (Levy, 2022).

The most common reported cause of anaphylaxis during general anaesthesia or postoperatively are NMBAs, which are responsible for 60% to 70% of episodes of anaphylaxis occurring during this period (Mali, 2012). NMBAs are usually administered during anaesthesia to facilitate endotracheal intubation and/or to improve surgical conditions. NMBAs may decrease the incidence of hoarseness and vocal cord injuries during intubation, and can facilitate mechanical ventilation in patients with poor lung compliance. The NMBAs most commonly implicated are succinylcholine (known as suxamethonium), rocuronium, atracurium, vecuronium, pancuronium, mivacurium, and cisatracurium. Allergy to NMBAs is more common in women than men, with three of four reactions occurring in females (Levy, 2022). The rate of NMBA anaphylaxis shows marked geographical variation in patients who have had no known prior exposure to NMBAs (Brusch, 2014).

NMBAs can cause anaphylaxis through both IgE-mediated and nonimmunologic, direct mast cell activation. There may be a specific receptor on mast cells activated by NMBAs as well as other drugs, such as fluoroquinolones and vancomycin. This receptor is designated Mas-related G-protein coupled receptor X2 (MRGPRX2) and has the capability of binding to a variety of ligands, resulting in mast cell activation clinically resembling an immune response. Reactions resulting from IgE-mediated allergy generally are less common, although usually more severe, than reactions due to other mechanisms. IgE sensitization is believed to occur due to cross-reactive tertiary or quaternary ammonium groups found in both NMBAs and a variety of topical cosmetics and personal products, as well as certain medicines, such as pholcodine. These ammonium groups are highly immunoreactive, multivalent epitopes, which can induce specific IgE antibodies. Sensitization through exposure to nonmedication agents may explain why allergic reactions to NMBAs occasionally occur upon initial exposure (Ledford, 2022).

The evaluation of suspected perioperative anaphylaxis involves a verification that the reaction was clinically consistent with anaphylaxis, clinical history, review of records of the event, analysis of laboratory tests obtained at the time, and skin testing or in vitro serum-specific IgE testing if the reaction was believed to be IgE-mediated. Skin testing and challenge procedures to identify drug

allergy should be performed by allergy specialists trained in the safe performance and accurate interpretation of these tests and manoeuvres (Ledford, 2022).

Pholcodine is an opiate with central antitussive and it is thought to induce immunologic stimulation in exposed individuals. The consequence of such IgE sensitisation in general is not known, but this raised the concern that patients may be put at risk of allergic reactions and even anaphylactic reaction to other substances, particularly allergens with a quaternary ammonium ion e.g. NMBAs. This theory is known as the pholcodine hypothesis. Throughout the years several studies have been published by the same group of authors (Florvaag et al) investigating the increased prevalence of IgE antibodies to pholcodine, morphine and suxamethonium, and ultimately higher incidence of IgE-mediated anaphylactic reactions to NMBAs in Norway. However, while these studies demonstrated potential effect of pholcodine use on the occurrence of NMBA related anaphylaxis, it should be noted that the studies relied on the number of spontaneously reported cases of NMBA related anaphylaxis. The observed decrease in the number of reported cases of NMBA-related anaphylaxis could be result of less reporting, changes to clinical practice, change in type of NMBA use, etc.

The most relevant publication from the literature is that of Sadleir et al (2021). In this case-control study from Australia, authors described that obesity is a risk factor for NMBA-related anaphylaxis and the risk increases with BMI grade. The authors also concluded that consumption of pholcodine is an independent and statistically significant risk factor for NMBA anaphylaxis (OR = 12.0; CI = 3.75-43; p-value < 0.001). However, several limitations in this study were identified, such as representativeness of patient population, recall bias to pholcodine exposure, possible misclassification of cases, different use of NMBAs than in the EU and power of the study. Nevertheless, the data from this study which was assessed in a separate regulatory procedure (PSUSA assessment) led to the inclusion of warning in the section 4.4 of the summary product characteristics (and section 2 of the package leaflet) of pholcodine-containing medicinal products and establishing of a potential risk.

The findings of the ALPHO study add to the cumulating evidence that there is a plausible causal relationship between pholcodine use and NMBA-related anaphylaxis and pholcodine is an important risk factor for NMBA-related anaphylaxis. The study was specifically designed to investigate an association between pholcodine exposure and the risk of perianaesthetic anaphylactic reaction related with NMBAs following the referral procedure 2011. Additionally, ALPHO was a multicentric study conducted in the EU (France) with collection of data from a large and significant number of patients and therefore considered representative of the EU population. The primary results showed a statistically significant link between use of pholcodine during the 12 months preceding anaesthesia and risk of perianaesthetic anaphylactic reaction related to NMBAs (OR adjusted=4.2 CI 95% [2.5; 6.9]).

The main uncertainty about the risk observed is the detection of other factors associated with the risk of a peranesthesic anaphylactic reaction related to a NMBA, such as professional exposure to quaternary ammoniums. Significantly, more patients with professional exposure to quaternary ammoniums were included into case vs. control populations (approx. 5.4 vs. 19.8%, p < 0.0001). In the study, the case vs. control patients were paired according to age, sex, the NMBA type used, the amount of time passed since the anaesthesia and the geographical region. Additionally, in order to limit confounding, cases were matched to controls on sex, category of NMBA injected, geographic area and period of anaesthesia and the association between pholcodine exposure and risk of anaphylactic reaction was notably adjusted based on history of surgery and occupational exposure to quaternary ammoniums (cleaners, hairdressers). Nonetheless, the factor that was found to dramatically increase the risk (OR 6.07) of the peranesthesic anaphylactic reaction related to a NMBA - professional exposure to quaternary ammoniums – was significantly prevalent in matched case population, comparing with control population. There are some other study limitations, such as weak agreement between the results of the self-administered questionnaires and the medicinal histories, long period

before a surgical procedure to be taken into account in regard to pholcodine use (12 months), which meant that patient could forget the fact of using pholcodine-containing medicinal product or, in opposite, state that pholcodine-containing medicinal product was used by mistaking it with another product.

From the review of the study, question arises whether pholcodine exposure was adequately established, both for controls and cases. Patients needed to recall their use of pholcodine in the period of one year, i.e. use of pholcodine could not be easily identified via prescription/dispensing data. The period of one year based on diminishing levels of IgE is acceptable, although it is noted that it might introduce a significant recall bias. Overall, when assessing pholcodine exposure, a small overlap between pholcodine exposure confirmed by self-administered questionnaire and pharmacy dispensary data was achieved. For only 21 exposed patients, both sources were positive (self-administered questionnaire and the dispensing pharmacist's medical history). This could be explained, as authors proposed, by the fact that patients used phocodine products already available at home, possibly dispensed for other family member or someone else could have given it to them. Or dispensary data was not retrieved from all pharmacies where patients could have received the medicine. Also, it could be argued that patients suffering more often from respiratory infections were likely to recall the use of pholcodine. Study authors performed evaluation of the impact of taking into account different sources of information for the estimation of pholcodine exposure (self-administered questionnaires, medical history of the dispensary pharmacist(s), electronic pharmaceutical file) on the occurrence of NMBA related anaphylaxis. In case both sources were positive, a significant association was seen (OR adjusted=11.03 CI 95% 3.09 - 39.40), however due to small number of cases the confidence interval is considered wide indicating less precision and study is underpowered.

Despite the above described limitations it is considered that the ALPHO study was adequately designed and supports that pholcodine is identified as an independent risk factor for NMBA-related anaphylaxis.

Additionally, the PRAC noted that two concerned MAH in their responses to the PRAC LoQ concluded that the benefit-risk balance of their concerned pholcodine-containing medicinal products is no longer favourable in view of the safety data available especially regarding the risk of anaphylaxis to NMBAs, the indication of pholcodine and the existing therapeutic alternatives.

The PRAC also noted the potential use of pholcodine in the context of the treatment of dry cough in COVID-19 patients in some Member States, and considered that these patients may be at risk of NMBA-related anaphylaxis in the event of progression to a severe form of COVID-19 requiring admission of the patient to the intensive care unit.

2.2.4.1. Risk minimisation measures

Several MAHs proposed to minimise this risk through:

- Revision of the product information (PI) to include more detailed information on the possible risk of cross-sensitization with pholcodine. More specifically, new detailed wording for section 4.4 of the SmPC with two key messages was suggested: (1) clinicians should inquire patients on the exposure of pholcodine in the last 12 months, prior to procedure; (2) in case of confirmation of previous use to pholcodine containing medicinal product, then serum specific IgE antibodies to quaternary ammonium ions/pholcodine and/or skin tests should be performed, prior to procedure.
- Introduction of a contraindication for pholcodine in case of previous allergic reaction to NMBAs in section 4.3 of the SmPC.
- Change in the status of pholcodine–containing medicines to ‘prescription-only’.

- Patient alert card as an additional risk minimisation measure (RMM) in order to ensure that special information regarding patient important risk to be communicated prior to any operative procedure and that patient alert card is held by patient at all times in order to reach the relevant HCP when needed.
- Direct health care professional communication (DHPC) as an additional RMM to inform HCPs of cross-sensitisation between pholcodine containing medicinal product and NMBA and the need to take certain actions and cautiously adapt their practices in relation to a previous pholcodine-containing medicinal product consumption.

To note, some MAHs have stated in their responses that any RMMs should focus on the use of NMBAs in clinical practice, rather than the use of pholcodine and suggested updating the PI of NMBAs with information regarding possible risk of cross-sensitization with pholcodine. Additionally, some of stakeholders who provided input suggested that more detailed information regarding potential anaphylaxis should be provided in the product information of pholcodine-containing medicinal products and of NMBAs. These proposals were also acknowledged by PRAC.

Each of the RMMs proposed were discussed by PRAC and overall are not considered effective measures to reduce the risk of perianaesthetic anaphylactic reaction related to NMBAs in patients previously exposed to pholcodine. To start, inclusion of contraindication in case of previous allergic reaction to NMBA in the product information of pholcodine-containing medicinal products would not minimise the risk. Patients can develop an allergic reaction to NMBA even if not previously exposed to an NMBA. Moreover, this contraindication would not prevent an event from happening. Likewise, inclusion of warning in the product information regarding previous pholcodine use is also not considered an effective measure, since patients or HCPs, could be unaware of the use, especially in the last 12 months.

Similarly, as other measures, measure of restriction of indication (to second line treatment, for example) and change of prescription status to 'prescription-only', although trying to limit patient population using pholcodine, still do not limit the risk in the population who used or is using pholcodine. PRAC considered the restriction of the indication to a second line treatment and is of the view that pholcodine in second line treatment will reduce the usage, but not reduce the risk of perianaesthetic anaphylactic reactions related to NMBAs. Thus, while restricting the indication would minimise the number of patients using pholcodine, this would not minimise the risk for the individual patient. Likewise, PRAC discussed the change of the legal status of the pholcodine-containing medicinal products to prescription-only medicines and it was similarly concluded that this measure would only limit the use of pholcodine but would not limit the risk. In addition, it is noteworthy that the ALPHO study was conducted in France where pholcodine-containing medicinal products are available as prescription-only medicines since April 2011. Based on the available data, pholcodine is currently available as a prescription-only medicine in the majority of Member States where it is authorised, therefore the situation in place reflects mainly the risk associated with the use of prescription-only products.

In regard to the patient alert card, this tool is also not considered an effective measure since pholcodine is used as a short-term acute treatment. Therefore, it is not expected for the patient to hold a card months after pholcodine treatment has stopped. Additionally, as an additional RMM, a DHPC would have impact in terms of information provided but would not minimise the risk. For instance, during pre-anaesthetic interviews, even if anaesthesiologists are well informed about the risk, it will not help them in their practice as they cannot predict which patients will develop cross-sensitization and reactions to NMBA. Also, patients might not recall if they were exposed to pholcodine in the last 12 months.

On another matter, PRAC noted that from the ALPHO study, it appears that measuring the presence of specific IgE antibodies to pholcodine could not be used to establish a potential for NMBA-related anaphylaxis as a precautionary measure. Besides, it is not considered as a feasible approach in many clinical settings such as in emergency situation, in which NMBAs are frequently administered.

Lastly, risk factors that would help to be taken into account to mitigate the risk could not be identified from the existing data by PRAC. Based on current data, no other mitigations to manage the risk could be proposed (such as recommendation of more specific than a 12-month time period between pholcodine usage and anaesthesia and dose or number of treatments with pholcodine) for those exposed to pholcodine. NMBAs are usually administered during anaesthesia, also in acute conditions when it might be impossible to rapidly gather information from the patient regarding the past use of pholcodine. Also, before the planned surgery to gather this information is challenging – patients usually do not remember all medicinal products they have used. Moreover, clinically doable tests to predict anaphylaxis with NMBAs after the use of pholcodine are not available. As no patient specific risk factors associated with pholcodine-induced NMBA sensitization is identified, and as it is not possible to predict who will need anaesthesia in the future, any patient treated with pholcodine will potentially be at risk of perianaesthetic anaphylaxis related with NMBAs.

Considering the NMBA use, and the proposals to update the PI for these products, it is important to note that decision to use a NMBA during anaesthesia is based on clinical necessity and cannot be avoided in any subpopulation, regardless of history of pholcodine use. Additionally, investigating pholcodine use prior to anaesthesia is likely to be unfeasible, as the majority of patients either will not know or will not remember that they have taken pholcodine-containing medicinal products. In addition, in a real-life situation where specialists are unable to take this factor into account in clinical practice, investigation of the pholcodine use in individual patients prior to anaesthesia is not considered to be of benefit as it will not change anaesthetic practice.

2.3. Data on efficacy

Available data on the efficacy of pholcodine is limited. A review of 9 clinical studies published in the scientific literature was conducted. Eight out of the nine studies identified were conducted between 1957 and 1986. Additionally, the number of available studies that used arms with pholcodine alone and those that compared it with a placebo is low (three studies described in two manuscripts, with a total of 73 participants). Also, pholcodine was used in combination products making it not possible to attribute any observed effect solely to pholcodine. Most of the studies were not sufficiently controlled, neither with active medicinal products nor a placebo, and some were conducted with associated products. The number of subjects was often limited and there was no objective criteria and recognised cut-off point for the reduction in cough. No study has been conducted on the long-term effects of pholcodine. However, this is an intrinsic issue of pholcodine, since it is an old substance for which trials have been conducted in line with the previously applicable standards.

Clinical trials have shown the antitussive efficacy of pholcodine to be superior to that of codeine, of longer duration, with an equivalent or safer toxicity profile, and with no risk of addiction (Blanchard, 2013). The most recent study (Equinozzi, 2006) showed efficacy of a 3-day course of pholcodine similar to that of dextromethorphan in the treatment of adult patients with acute, non-productive cough. Although the study had its limitations owing to the lack of a placebo control arm and the non-validated and subjective nature of the results (frequency and intensity of cough), an effect was observed soon after the treatment was administered.

All these results suggest the efficacy of pholcodine in the treatment of acute non-productive cough. In comparative studies, pholcodine appears to be at least as effective as dextromethorphan or codeine

with a longer duration of antitussive action related to its pharmacokinetic properties. Also, during previous referral procedure in 2011, the CHMP concluded that the existing data, covered also within this assessment is consistent and supportive of the efficacy of pholcodine in the treatment of acute non-productive cough. As conclusion, no new efficacy data about benefits of treatment of pholcodine have been identified, therefore efficacy of pholcodine in treatment of non-productive cough is considered unchanged.

3. Stakeholders input

Written submissions were also received from stakeholders. All data submitted was considered by the PRAC in reaching its conclusions.

The stakeholders noted dry irritative cough as a potential health problem, with significant impact on patient's quality of life, which requires treatment with effective antitussive medications. Notably, in view of several HCPs who provided input, pholcodine is one of the most effective antitussive medicines in comparison to other medicinal products available on the market in Croatia and Slovenia with no serious adverse drug reactions reported.

Additionally, some of the stakeholders stated that more detailed information regarding potential anaphylaxis would need to be provided in the product information of pholcodine-containing medicinal products and of NMBAs. The stakeholders also considered that the risk should also be communicated wider. The update of the product information should also include populations at higher risk for anaphylaxis reactions (underlying diseases, exposure to environmental factors, medicinal products that modify immune response etc.), so that patients that are not at high risk of possible anaphylaxis could still benefit from pholcodine.

4. Benefit-risk balance

The totality of available data suggests that the efficacy of pholcodine-containing medicinal products in symptomatic treatment of non-productive cough is considered established considering the marketing authorisations for these medicinal products as well as the conclusions on efficacy in the previous CHMP referral in 2011. No new efficacy data became available since the previously mentioned referral. In terms of the overall safety profile of pholcodine, the majority of adverse drug reactions belong to gastrointestinal and psychiatric disorders, similarly as for other opioids. However, throughout the years, case reports and results from studies raised the concern that patients treated with pholcodine may be put at risk of allergic reactions and even anaphylactic reaction to other substances, particularly allergens with a quaternary ammonium ion e.g. NMBAs.

Concerning this risk, in 2011, the CHMP conducted a review and considered that the evidence of a link between pholcodine and NMBA-related anaphylaxis was circumstantial and not entirely consistent. CHMP, nevertheless, concluded that further investigation on the possibility of an association between pholcodine use and NMBA-related anaphylaxis was needed. As an outcome of the referral, the conduct of a PASS (post-authorisation safety study) was imposed. The results of such study, named ALPHO, became available in 2022 and were thoroughly assessed in the present safety review. The results from the ALPHO study showed a statistically significant link between use of pholcodine during the 12 months preceding anaesthesia and risk of perianaesthetic anaphylactic reaction related to NMBAs (OR adjusted=4.2 CI 95% [2.5; 6.9]). Despite some identified study limitations, the data from this study show an association between the risk of NMBA-related anaphylaxis and previous pholcodine use that cannot be refuted by other effects or biases. Moreover, the findings of the ALPHO study add to the cumulating evidence from literature reports and previous epidemiological studies that pholcodine is an important risk factor for NMBA-related anaphylaxis. Therefore, PRAC is of the view that based on the

totality of evidence a causal relationship between pholcodine use and NMBA-related anaphylaxis is considered sufficiently established.

It should be also highlighted, that despite the low number of documented cases of anaphylaxis specifically against pholcodine, perioperative anaphylaxis (including anaphylaxis to NMBAs) is a serious and life threatening medical condition which is rare (1/10.000 anaesthesia procedures) but with relatively high mortality (4-6%). Therefore, all available measures should be taken to decrease its incidence. As discussed in section 2.2.4, it is noted that a broader range of agents can induce cross-sensitization to NMBAs and cause NMBA-related anaphylaxis. In the ALPHO study, exposure to such agents was a confounding risk. The exposure to these agents, such as occupational exposure to quaternary ammonium ions for example, however may not be possible to identify nor to fully prevent or minimise. Based on the evidence reviewed, pholcodine is identified as a risk factor for NMBA-related anaphylaxis regardless of other risk factors. Importantly, epidemiological studies indicate that numbers of perioperative anaphylaxis cases are significantly reduced after pholcodine-containing medicinal products were removed from the market. This is supported by a study conducted in Norway, when six years after withdrawal of pholcodine-containing medicinal products from the Norwegian market, the Norwegian population became significantly less IgE sensitized and clinically more tolerant to NMBAs (De Pater, 2017). These results indicate the possible impact of acting upon the pholcodine usage.

In the context of the procedure and facing the evidence reviewed and noted above, PRAC discussed potential measures which would minimise the risk of NMBA-related anaphylaxis to an acceptable level such as restriction of indication, PI updates, change to prescription-only status, patient alert card and dissemination of DHPC. Overall, the RMMs are not considered by PRAC appropriate and effective measures to reduce the risk NMBA-related anaphylaxis in patients previously treated with pholcodine to an acceptable level. In general, the RMMs discussed would increase HCPs and patient awareness of the existing risk (e.g., SmPC changes, DHPC, patient alert card) or would reduce the number of the patients using pholcodine (e.g., restriction of indication or change of legal status). However, these measures would not minimise the risk of NMBA-related anaphylaxis for an individual patient exposed to pholcodine. Moreover, the decision to use a NMBA during anaesthesia is based on clinical necessity and cannot be avoided in any subpopulation, regardless of the history of pholcodine use. Therefore, patients exposed to pholcodine would still be at risk of NMBA-related anaphylaxis, which is regarded as serious, unpredictable and life threatening. PRAC could also not identify measures that would allow HCPs to identify which patients treated with pholcodine will develop cross-sensitization and reactions to NMBAs. Further, the PRAC could not identify condition(s) which if fulfilled would demonstrate a positive benefit-risk balance for these products in a defined patient population. Lastly, PRAC noted that other therapeutic alternatives for treatment of non-productive dry cough are available in the EU MS, such as codeine, ethylmorphine, dextromethorphan, butamirate and others.

Therefore, the PRAC concluded that the risk of perianaesthetic anaphylactic reaction related to NMBAs outweighs the benefits of pholcodine-containing medicinal products in treatment of non-productive cough, a symptomatic indication considered acute and not serious.

Consequently, the PRAC recommended the revocation of the marketing authorisations for pholcodine-containing medicinal products.

5. Risk Management

The Committee, having considered the data submitted in the procedure was of the opinion that no feasible and proportionate risk minimisation measure would reduce the risks to an acceptable level (see section 2.2.4.1 for details on the measures reviewed).

5.1. *Direct Healthcare Professional Communications and Communication plan*

The Committee adopted the wording of a DHPC, to inform HCP of the conclusions of the review and therefore the upcoming unavailability of pholcodine-containing medicinal products. The Committee also agreed on a communication plan.

6. Grounds for Recommendation

Whereas,

- The PRAC considered the procedure under Article 107i of Directive 2001/83/EC for pholcodine-containing medicinal products.
- The PRAC reviewed the totality of the data available for pholcodine-containing medicinal products in relation to the risk of perianaesthetic anaphylactic reaction related to NMBAs, in writing and in an oral explanation. This included the results of observational studies (including the ALPHO study), literature data, post-marketing case reports as well as responses submitted by the MAHs and the submissions by the stakeholders.
- The PRAC considered that the data reviewed confirm an association between the use of pholcodine and the risk of perianaesthetic anaphylactic reaction to NMBAs, an unpredictable and potentially life-threatening situation.
- No specific characteristics for perianaesthetic anaphylactic reaction to NMBA could be identified in patients who have been treated with pholcodine, and therefore all these patients are considered at risk. In addition, the PRAC could not identify risk minimisation measures that would be effective at reducing the risk of perianaesthetic anaphylactic reaction related to NMBAs in patients who have been treated with pholcodine-containing medicinal products.
- The PRAC therefore concluded that the risk of perianaesthetic anaphylactic reaction related to NMBAs outweighs the benefit of pholcodine in the treatment of non-productive cough, a symptomatic indication considered acute and not serious.
- Further, the PRAC could not identify conditions which if fulfilled would demonstrate a positive benefit-risk balance for pholcodine-containing medicinal products in a defined patient population.

The Committee, as a consequence, considers that the benefit-risk balance of pholcodine-containing medicinal products is not favourable.

Therefore, pursuant to Article 116 of Directive 2001/83/EC, the Committee recommends the revocation of the marketing authorisations for pholcodine-containing medicinal products.

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Appendix 1

Divergent positions to PRAC recommendation

Procedure under Article 107i of Directive 2001/83/EC

Pholcodine containing medicinal products

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

Divergent statement

The below named PRAC Members consider the benefit-risk balance of pholcodine-containing products negative, however do not consider that revocation is a risk proportionate measure taking into account limitations of available evidence from ALPHO study (i.e. power of the study, issue of identifying exposition to pholcodine, validity of final analysis model) and that a feasible condition for lifting the suspension can be identified. Benefit-risk balance of pholcodine-containing products could be reconsidered in case of identification of subpopulation in which risk of sensitisation to neuromuscular blocking agents (NMBAs) due to pholcodine use is adequately minimised, such as patients with certain conditions who are unlikely to receive a NMBA.

PRAC Members expressing a divergent opinion:

- Nikica Mirošević Skvrce (Croatia)
- John Joseph Borg (Malta)