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## Assessment report for Pholcodine containing medicinal products

Procedure number: EMEA/H/A-31/1292

Referral under Article 31 of Directive 2001/83/EC, as amended

Assessment Report as adopted by the CHMP with all information of a commercially confidential nature deleted.



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# 1. Background information on the procedure

## 1.1. Referral of the matter to the CHMP

On 28 January 2011, France triggered a referral under Article 31 of Directive 2001/83/EC, as amended. The CHMP was requested to give its opinion on whether the marketing authorisations for medicinal products containing pholcodine-containing medicinal products should be maintained, varied, suspended or withdrawn.

The AFSSAPS concerns arose from the potential risk that pholcodine may lead to IgE-sensitisation to neuromuscular blocking agents (NMBAs). Literature has been published suggesting a link between pholcodine consumption and cross sensitisation to NMBAs, resulting in anaphylactic reactions during surgery. The published data refers mainly to Norway and Sweden, where pholcodine is no longer marketed. In France, data from spontaneous reporting suggests a 25% increase in the number of anaphylactic shocks to NMBAs in the period 2008/2009 when compared to the 2003/2004 period. This coincides with a 9% increase in the consumption of pholcodine-containing products in France between the two periods. As a consequence, the French Medicines Agency changed the prescription status of pholcodine-containing medicines to prescription only and triggered this referral.

The procedure described in Article 32 of Directive 2001/83/EC, as amended, was applicable.

# 2. Scientific discussion

## 2.1. Introduction

Pholcodine is an opiate with central antitussive action used for treatment of cough and cold symptoms in children and adults. 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.

In Sweden, during 70's and 80's, one single pholcodine containing-product was marketed. Tablet form was withdrawn in 1985 and syrup form in 1989, following therapeutic recommendations for the management of cough which were in favour of the use of other products. The number of anaphylactic reactions after exposure to NMBAs was significant in 70's, whereas no cases were reported after 1990.

In Norway, in March 2007, the Marketing Authorisation Holder (MAH) of the single cough suppressant product containing pholcodine voluntarily withdrew the product from the market.

In 2009, an article was published by a Swedish/Norwegian team of researchers reporting that withdrawal of pholcodine containing products in Sweden and Norway resulted in a decrease in reports on NMBA-related anaphylaxis<sup>1</sup>. The same team of researchers have published a number of other papers on the correlation between pholcodine consumption and IgE levels. In publications dated 2010<sup>2</sup> and 2011<sup>3</sup>, the authors conclude that the withdrawal of pholcodine resulted in a lower frequency of NMBA-suspected anaphylaxis and that continued use of medicinal products containing this substance should be questioned.

Pholcodine is currently approved in the EU in Belgium, France, Ireland, Lithuania, Luxembourg, Malta, Slovenia, Spain and United Kingdom, either subject to medical prescription or as non-prescription medicines.

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<sup>1</sup> Johansson SGO et al. Pholcodine caused anaphylaxis in Sweden 30 years ago. *Allergy* 2009; 64: 820-821

<sup>2</sup> Johansson SGO et al. National pholcodine consumption and the prevalence of IgE-sensitisation; a multicenter study. *Allergy* 2010 Apr; 65 (4): 498-502.

<sup>3</sup> Florvaag E, Johansson SGO, Irgens Å, de Pater GH. IgE-sensitisation to the cough suppressant pholcodine and the effects of its withdrawal from the Norwegian market. *Allergy* 2011; 66: 955-960.

## 2.2. Safety

In order to assess the general safety of pholcodine, relevant information from pre-clinical studies, clinical trials, post-marketing spontaneous case reports, pharmacoepidemiological studies and published literature was assessed. Particular attention was dedicated to the issue of IgE sensitisation and the possibility of an association with anaphylactic reactions to NMBAs.

### 2.2.1. Results

#### Pre-clinical data

Limited pre-clinical data is available on pholcodine. Compared to codeine, pholcodine has been estimated to be 5-7 times less toxic in mice and is therefore considered to be safer than codeine. Pholcodine has been found to have a greater respiratory and cardiovascular depressant effect in some animal species, but such effects have not been seen in man at therapeutic levels.

In some studies pholcodine was reported to be 3 times more effective at blocking mechanically induced cough reflex in anaesthetised cats compared to codeine, but it was weaker at inhibiting chemically induced cough. Pholcodine seems to have differing efficacy compared to codeine depending on the animal model it is tested in. It also seems to be as potent as codeine at eliciting side effects in animal models.

#### Clinical data

##### **Equinozzi and Robuschi (2006)**

The aim of this study was to compare the efficacy and tolerability of pholcodine with that of dextromethorphan, in patients with acute non-productive cough. Adult subjects were treated with either 19.65 mg pholcodine or 19.95 mg dextromethorphan bromidrate three times a day. Only 17 of the 129 patients reported adverse events: 6 patients with pholcodine and 11 patients with dextromethorphan. The most frequently reported adverse reactions with both pholcodine (4.8%) and dextromethorphan (7.6%) were related to the gastrointestinal system (upper abdominal pain, diarrhoea, dyspepsia, nausea and vomiting). No serious adverse events were reported and no adverse event required additional treatment. All were resolved within 2-3 days. Treatment was discontinued in one pholcodine patient due to upper abdominal pain and in three dextromethorphan recipients because of vasovagal syncope and vomiting (n=1), vomiting (n=1) and asthenia and somnolence (n=1). In the investigator-rated global tolerability scores, 45.2% and 31.3% of pholcodine and dextromethorphan recipients, respectively, were rated as 'excellent' and 1.6% and 3.1% were rated as 'poor'. Pholcodine had significantly better tolerability than dextromethorphan (OR 2.18; 95% CI 1.03, 4.63; p=0.041). There was no placebo control group included in this trial. The authors concluded that both dextromethorphan and pholcodine were well tolerated with a slightly lower incidence of adverse events with pholcodine than dextromethorphan.

##### **Heffron (1961)**

Fifty four (54) male inmates ranging in age from 21 to 65 years were included in this study. Nineteen (19) of the patients suffered from acute cough. Among them, two patients complained of nausea, including one who refused medication after the second day. In the other, nausea subsided after the first day of therapy. A third patient reported a 'burning sensation' in chest and throat, not serious enough to interfere with therapy. Thirty-five (35) patients had chronic cough. Among them, complaints of side effects were more frequent but confined to the first days of treatment. These included 6 complaints of 'gas' and nausea, one of diarrhoea and anorexia and three of anorexia with 'gas' or nausea. None was sufficiently serious to warrant discontinuation of therapy. Several patients in both groups reported a slight tranquilizing effect. Treatment had to be stopped in 7 subjects, however these were all former narcotic addicts and 5 of the 7 had received 80 mg pholcodine or more per day over a 3 to 4 month period. No withdrawal effects were reported upon cessation of the treatment.

##### **Mulinos (1962)**

In this study subjects used pholcodine at a dose of 10 or 20 mg, 2 to 4 times a day for up to 29 days. When pholcodine or codeine was swapped for the placebo, subjects did not report a desire for the previous medications. There were also no reports of withdrawal symptoms.

### **Rose (1967)**

The trial preparation contained 15 mg pholcodine and 60 mg pseudoephedrine per dose. The control preparation consisted of 15 mg of codeine phosphate per dose. A total of 45 patients took part in the trial, all with some degree of chronic respiratory disease. One patient complained only of breathlessness and two only of cough, whilst the remainder suffered to a greater or lesser extent from both. Each patient received each preparation for one month. Ten (10) patients experienced one or more side effects with the pholcodine preparation, including 6 reports of nausea, 2 of sleeplessness, 2 of constipation and one of bitter taste. Eight (8) patients had side effects on the control linctus, including one report of sleeplessness, 3 of nausea, 3 of constipation, one of chest pain and one of flatulent dyspepsia. The level of severity was not reported.

### **Kelly (1963)**

In this comparative single-blind study, 53 children between 8 months to 17 years with acute cough with upper respiratory infections as the underlying cause were treated with either pholcodine 5 mg or codeine 8 mg during 5 days approximately. One patient in the pholcodine group, a 10 year old girl with influenza bereaving her mother vomited when administered the first dose of medication. Medication was immediately discontinued. In the codeine group, 8 patients complained of mild constipation.

### **Jaffe and Grimshaw (1983)**

In a large trial of 217 children between 6 and 12 years old, a pholcodine-containing combination product (paracetamol 150 mg, pholcodine 5 mg, phenylpropranolamine 12.5 mg, per 5 ml) or another combination product not containing pholcodine (codeine phosphate 10 mg, triprolidine hydrochloride 1.25 mg, pseudoephedrine hydrochloride 30 mg, per 5 ml) were given for 3 days. The parents of the subjects were asked to record side effects such as drowsiness, tremor, tachycardia, nausea and anorexia. In the pholcodine group, 28 children reported drowsiness, 8 reported nausea and there were 8 cases of anorexia. Two children complained of tremor and 3 of heartburn, all 5 cases occurring in the codeine group. The most significant difference between the groups involved drowsiness, where there was higher incidence in children taking the codeine preparation ( $\chi^2=16.67$ ;  $p<0.001$ ); in the pholcodine group, 74 (70.5%) children were free from side effects compared with 43 (39.4%) children in the codeine group. This difference was significant ( $\chi^2=20.91$ ;  $p<0.001$ ).

No adverse events have been observed in study Edward and al (1977) which enrolled 24 patients with chronic bronchitis.

#### Post-marketing data

Data made available by some of the concerned marketing authorisation holders on post-marketing adverse event reports was analysed. The majority belonged to the system organ class (SOC) 'skin and subcutaneous tissue disorders', and included reports of rash, erythema, pruritus and angioedema. Among the reports of angioedema, in one case there was a positive test to pholcodine and in 2 cases there was positive rechallenge. Events of interest in this SOC also included 1 case of Stevens Johnson syndrome, 1 case of toxicoderma, 4 cases of erythema multiforme and 2 cases of toxic epidermal necrolysis, although very limited information was available for these cases.

Reports in the 'immune system disorders' SOC consisted mainly of hypersensitivity and anaphylactic reactions. The majority of these cases were serious and in several of them allergic tests were positive to pholcodine, or there was positive rechallenge.

There were also reports of adverse events in the 'gastrointestinal disorders' SOC (including nausea, vomiting, constipation) and in the 'respiratory, thoracic and mediastinal disorders' SOC (including cough and difficulty breathing), the majority of which was not serious. There were a few cases in this SOC with a fatal outcome, but assessment of these is confounded by the presence of risk factors, concomitant medication and/or insufficient information.

Overall, the majority of adverse events spontaneously reported are in line with what would be expected of an opiate derivative.

### Literature data

A search in the literature for relevant safety information identified one case of angioedema with positive rechallenge and intradermal test results<sup>4</sup>. In addition a case report of acute generalized exanthematous pustulosis was identified<sup>5</sup>.

### The pholcodine hypothesis

Anaphylaxis that occurs during anaesthesia is a significant cause of perioperative morbidity and mortality. Reactions may be of immunologic (allergic) or non-immunologic origin. Most allergic reactions are IgE mediated.

The first articles on detection of specific IgE to NMBAs in subjects experiencing an anaphylactic reaction during anaesthesia were published in 1983. Baldo demonstrated that IgE specificities were turned to quaternary ammonium ions or tertiary amines and underlined that such ions were largely widespread (medicines, cosmetics, disinfectants, food, industrial materials, etc) and as a consequence, that patient cross-sensitivity was conceivable, which could explain the occurrence of allergic reaction to NMBAs in the absence of previous contact with these products.

In 2005, Florvaag E, Johansson SGO and al suggested a possible link between the consumption of pholcodine-containing syrups and the occurrence of anaphylactic reactions to the depolarizing NMBA suxamethonium. As Florvaag and colleagues observed that the occurrence of anaphylactic reactions to NMBAs was 6 times more common in Norway than in Sweden, they compared the prevalence of specific IgE to suxamethonium, pholcodine and morphine in samples of patients from both Sweden and Norway with suspected allergies, 500 blood donors from both countries and 65 Norwegian patients with documented anaphylaxis to NMBA. In addition, 84 different household chemicals were tested, by IgE antibody inhibition, for suxamethonium and morphine.

The researchers found that in Norway 0.4% of the blood donors, 3.7% of allergics and 38.5% of anaphylactics were IgE-sensitized to suxamethonium, and 5.0%, 10% and 66.7%, respectively, to morphine. No serum sample from Sweden was positive. The majority of those sensitized (69%) were women. From the analysis of the household chemicals it was established that several contained suxamethonium and/or morphine activity, but the only difference identified between Norway and Sweden was the existence in Norway of a cough syrup containing pholcodine. IgE antibodies to pholcodine were present in 6.0% of blood donors from Norway and in no serum from Sweden. Of the anaphylactics, 65-68% were sensitized to morphine or pholcodine but only 39% to suxamethonium.

In 2006 and 2007, the same Scandinavian authors suggested that pholcodine acts as a stimulant of allergy ("booster effect"). In a pivotal study, pholcodine ingestion both stimulated total IgE and specific IgE production to pholcodine, morphine and suxamethonium. Other subjects who were exposed to domestic products did not present increased IgE. The research team has also referred to WHO data indicating that some countries with high consumption of pholcodine (Australia, France, Ireland) also have a high incidence of anaphylactic shock due to NMBAs. These data also seemed to indicate that a low number of anaphylaxis cases are reported in countries where pholcodine is not marketed (Denmark, Germany, Netherlands, Sweden).

In 2007, the authors reported that 17 randomised subjects with history of NMBA-related anaphylactic reaction were exposed to an antitussive syrup containing either pholcodine or guaifenesine, and a significant increase in total IgE and specific IgE to pholcodine, morphine and suxamethonium was only observed in the group exposed to pholcodine. Elevations of to pneumallergens (Phadiatop test) and food allergies (F<sub>x</sub>5 test) were also noticed.

In March 2007, in Norway, the MAH of the only medicinal product containing pholcodine voluntarily requested the withdrawal of the marketing authorisation for the product.

In 2009, Florvaag and al. performed analyses on Swedish serums taken between 1970 and 1999 and found a high prevalence of specific IgE to pholcodine, morphine and suxamethonium in samples dated from the 70's and 80's, a time at which one product containing pholcodine was marketed in Sweden. The tablet form was withdrawn from the Swedish market in 1985 and syrup form in 1989, due to a

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<sup>4</sup> Codreanu F: Allergy. 2005 Apr; 60(4):544-5. Allergy to pholcodine: first case documented by oral challenge. Codreanu F, Morisset M, Kanny G, Moneret-Vautrin DA. Department of Internal Medicine, Clinical Immunology and Allergology University Hospital, Nancy, France.

<sup>5</sup> Stephen Lee, Austr Jr of Dermatology; 1995

change in therapeutic recommendations for cough management which favoured other substances. They also described a decrease in specific IgE prevalence in samples from the 90's. The authors reported that the number of anaphylactic reactions following NMBA exposure was elevated in 70's, whereas no cases were reported after 1990.

This study aimed to demonstrate the impact of pholcodine withdrawal on the number of anaphylactic reactions related to NMBAs; however, the study raised the question of specific IgE persistence in plasma. Indeed, even if the IgE prevalence decreased rapidly after pholcodine withdrawal, it would be expected that in some patients reactions would continue to occur. However no reactions were reported after 1990 in Sweden.

In 2010, Florvaag and colleagues published the results of an international study which aim to assess the relationship between pholcodine consumption in several countries (DE, DK, FI, FR, NL, NO, SE, UK, USA) and prevalence of specific IgE (pholcodine, morphine, suxamethonium, NMBAs) in 200 atopic (positive Phadiatop test) subjects per country, in a total 1800 subjects. The results showed that the relationship between pholcodine consumption and the prevalence of IgE sensitisation to pholcodine and morphine was significant (but this was not observed for suxamethonium). However, this relationship was weakened by data from the Netherlands and USA, where the prevalence of IgE to pholcodine and morphine was elevated in spite of the fact that no pholcodine-containing product is marketed.

In 2011, Florvaag and al published another article, this time describing the prevalence of IgE and anaphylactic reactions during anaesthesia in the years following the withdrawal of the only pholcodine-containing product in Norway. The authors concluded that withdrawing pholcodine significantly lowered, within 1-2 years, the levels of IgE and IgE antibodies to pholcodine, morphine and suxamethonium and, within 3 years, the frequency of NMBA suspected anaphylaxis. The results, summarised in tables 1-3 below, were therefore considered by the authors to strengthen the pholcodine hypothesis and raise the need to question the existence of antitussive products containing pholcodine.

**Table 1 Prevalences of IgE sensitisation ( $\geq 0.35$  kU<sub>A</sub>/l) to pholcodine (PHO), morphine (MOR) and suxamethonium (SUX) in 'allergics' (n=300) sampled before and yearly up to 3 years after withdrawal of the pholcodine-containing cough syrup from the Norwegian market. The results are expressed as absolute numbers and, in parenthesis, percentages of positive samples.**

(in Florvaag E, Johansson SGO, Irgens Å, de Pater GH. IgE-sensitisation to the cough suppressant pholcodine and the effects of its withdrawal from the Norwegian market. Allergy 2011; 66: 955-960.)

	Before	Years after Tuxi <sup>®</sup> withdrawal			Trend	P-value	P-value Linear-by
		1	2	3			
PHO	33 (11.0)	15 (5.0)	17 (5.7)	8 (2.7)	-0.418	<0.001	<0.001*
MOR	30 (10.0)	nt	8 (2.7)	4 (1.3)	-0.667	<0.001	<0.001*
SUX	11 (3.7)	2 (0.7)	1 (0.3)	1 (0.3)	-1.066	0.002	<0.001*

MOR, morphine; PHO, pholcodine; SUX, suxamethonium; nt, not tested.

\*Exact methods.

**Table 2 Occurrences of elevated IgE (>120 kU/l) in percent of the total number of yearly analyses performed at the routine laboratory and related in time to the withdrawal of pholcodine in Norway, before (n=24096), after 1 year (n=24129), after 2 years (n=25806) and after 3 years (n=26491). 2006 was used as reference year for statistical analysis.**

	Per cent IgE >120 kU/l	Crude RR	95% CI	Adjusted RR*	95% CI
2006 before	25.3	1		1	
2007 after 1 year	26.3	1.04	1.01-1.10	1.04	1.01-1.07
2008 after 2 years	24.1	0.95	0.90-0.98	0.95	0.92-0.98
2009 after 3 years	21.5	0.92	0.77-0.85	0.88	0.84-0.91
Trend				0.81	0.001

\*Relative risk (RR) was adjusted for gender, age and month of analysis.

**Table 3 Linear trend of reported suspected anaphylactic reactions during general anaesthesia from the NARA registered yearly through 2005–2010. Shown are the total numbers of reported reactions and the number of reactions related to the use of NMBAs. In addition, the number of sera with IgE antibodies to SUX ( $>0.35 \text{ kU}_A/\text{I}$ ) measured at the time of reaction is listed (IgE SUX). For statistical analysis, the total number of general anaesthesias per year is set to 200 000.**

	2005	2006	2007	2008	2009	2010 first 6 month	Trend	P-value	P-value Linear by linear
Total	94	89	81	88	53	25	-0.116	<0.001	<0.001
NMBA	57	62	56	66	34	18	-0.089	0.020	0.018
IgE SUX	11	18	12	15	3	2	-0.198	0.021	0.017*

NARA, Norwegian Network for Anaphylaxis under Anaesthesia; NMBAs, neuromuscular blocking agents; SUX, suxamethonium.

\*Exact method.

## 2.2.2. Discussion

Limited safety data are available allowing for direct comparison between pholcodine and other opiates in clinical studies. No specific adverse events were identified with pholcodine that have not also been associated to codeine. No withdrawal symptoms were observed in the studies that evaluated the potential addiction to pholcodine.

Only one recent study compared pholcodine to dextrometorphan (Equinozzi and al, 2006) in a randomised and double blinded design in patients with acute non productive cough, and the most frequently reported adverse reactions with both pholcodine (4.8%) and dextromethorphan (7.6%) were related to the gastrointestinal system (upper abdominal pain, diarrhoea, dyspepsia, nausea and vomiting).

In other studies results on safety are similar. The main adverse events reported were related to the SOC 'gastrointestinal disorders' or 'psychiatric disorders' (anorexia, sleeplessness) as expected with opiate derivatives. The post-marketing data analysed is also consistent with these observations.

In recent years, observations in Norway led one team of researchers to raise the possibility that high consumption of cough mixtures in these countries was related to increased prevalence of IgE antibodies to pholcodine, morphine and suxamethonium, and ultimately higher incidence of IgE-mediated anaphylactic reactions to NMBAs. Based on immunological analyses determining the prevalence of antibodies to these active substances in different populations, and reporting rates for NMBA-related anaphylaxis during anaesthesia, researchers concluded that withdrawal of pholcodine from the market in Norway significantly lowered within 1-2 years levels of IgE and IgE antibodies to pholcodine, and within 3 years, the frequency of NMBA suspected anaphylaxis. Data from Sweden where pholcodine has not been marketed since the 80's is indicative, like in Norway, that the level of IgE-sensitisation to pholcodine has been decreasing over time in parallel to a decrease in the number of NMBA-related anaphylaxis cases<sup>6</sup>.

The evidence in support of an association between pholcodine and NMBA-related anaphylaxis derives from ecological studies conducted by a single research team relying on spontaneously reported adverse reactions to NMBAs. While the data from Sweden and Norway appears to be consistent, other factors may explain the observations. In recent years the Norwegian network for anaphylaxis under general anaesthesia, which collects these reports, has been subject to less intense promotion, and therefore it is possible that the observed decrease in reporting does not actually reflect lower occurrence. It is also noted that in Norway, although there is a lower number of anaphylaxis reports since pholcodine was withdrawn, the severity of the reactions reported has not changed. Class II and III reactions still represent the majority of the reported cases, same as when pholcodine was still marketed.

The absence of any report of IgE-mediated anaphylactic reaction to NMBAs in Sweden since 1990 raises further questions on the reliability of the data, as regardless of pholcodine use NMBAs would still be expected to cause anaphylactic reactions and the Swedish data does not appear to reflect this expected background rate.

<sup>6</sup> Johansson SGO et al. Pholcodine caused anaphylaxis in Sweden 30 years ago. *Allergy* 2009; 64: 820-821.

In countries with small populations such as Norway (4.8 million) and Sweden (9.3 million), confounding factors such as a change in anaesthetic procedures, type of products used in anaesthesia and overall use of NMBAs could play a role in explaining the findings.

Even assuming that there is some biological plausibility for the pholcodine-sensitisation and that the numbers reflect the actual prevalence of anaphylactic reactions during surgery, a broad range of other agents may also be responsible. If indeed other substances containing quaternary ammonium ions have the ability to induce cross-sensitisation to NMBAs, and if such substances can be found in numerous household products, the specificity of IgE to pholcodine has to be questioned. This could explain the reason why data from countries such as the USA or the Netherlands does not fit with the pholcodine hypothesis: in these countries pholcodine is not marketed, and still prevalence of IgE to pholcodine and morphine was found to be high. Ultimately, even if the prevalence of sensitisation is high, the clinical relevance of these findings is questionable.

A further issue for consideration is that anaphylactic reactions to pholcodine itself appear to be rare. Very few cases have been described with a substance that has been extensively used for decades and that is even available in some countries without medical prescription.

Thus the evidence in support of an association between pholcodine and NMBA-related anaphylaxis is circumstantial, not entirely consistent and does not support the conclusion that there is a significant risk of cross-sensitisation to NMBAs and subsequent development of anaphylaxis during surgery. Further data needs to be generated to clarify the possibility of an association between pholcodine use and NMBA-related anaphylaxis.

### **2.3. Clinical efficacy**

The first clinical studies on efficacy of pholcodine as an antitussive agent are dated 1950. The most recent study was published in 2006.

#### **2.3.1. Results**

##### Adults

##### **Equinozzi and Robuschi (2006)**

A multicenter, randomized, parallel group, controlled, double-blind study was conducted to compare efficacy and tolerability of pholcodine and dextromethorphan in the treatment of acute non-productive cough. This most recent study was conducted by the MAH Zambon between March and June 2005.

A total of 129 adults between 18 and 69 years of age (mean 45.8 years), being treated by 22 general practitioners in Italy for acute non-productive cough, were randomly assigned to receive 15 ml of commercially available linctus of either pholcodine (Biocalyptol linctus equating to 19.65 mg pholcodine) or dextromethorphan (Vicks Tosse Sedativo, equating to 19.95 mg dextromethorphan bronhydrate), three times a day for 72 hours. 35.5% and 25.8% of the patients respectively in the pholcodine and dextromethorphan group were smokers. Severe respiratory failure, bronchial hypersecretion, neoplasm, lower respiratory tract disease, tuberculosis and asthma were to be excluded.

Cough scores (on a 5-point scale) for night-time and daytime frequency and daytime intensity (mild, moderate or severe) were recorded at home on a diary card by the patients on each day of treatment. Due to the somewhat subjective nature of this measurement, the investigators also assessed and measured global efficacy as the change in symptoms on a 1 to 4 point scale at the final visit. At the final visit patients also recorded their perceived global efficacy and tolerability as either poor, fair, good or excellent. The primary endpoint was a change from base line cough frequency at day 3, on a 4 point scale from 1 (no change or worsening of symptoms) to 3 (improvement by >2 points).

The mean reduction in daytime cough frequency was 1.4 in the pholcodine group and 1.3 in the dextromethorphan group (per protocol population) (OR: 1.44; 95% CI: 0.73-2.82). The mean reduction in night-time cough frequency was 1.3 in both groups, and cough intensity reduction was 0.7

in the pholcodine group and 0.8 in the dextromethorphan group. There was statistical improvement from baseline for the three measurements with both treatments and improvements were similar.

Whilst this study has limitations such as the lack of a placebo control arm and the non-validated and subjective nature of the outcomes (frequency and intensity of cough), an effect was observed very early in the treatment which is consistent with a positive effect of pholcodine in acute non-productive cough.

### **Heffron (1961)**

This study assessed the efficacy and the addiction liability of pholcodine in 54 male prison inmates (ages 21 to 65 years) with cough associated to various conditions. Nineteen (19) had acute cough (in most cases non-productive) associated with respiratory infection (14 of which had severe cough and 5 had moderate cough) for an average of 3 weeks (2 days to 6 weeks). Thirty-five (35) had chronic cough including chronic bronchitis (19), bronchiectasis (7), arrested tuberculosis (5), pulmonary emphysema (3) and pulmonary carcinoma (1). Twenty-nine (29) of the 35 subjects had severe cough and 6 subjects had moderate cough. Most of the subjects in this group had been coughing for years with only 4 coughing for less than 1 year.

Subjects in the acute cough group were given 5 or 10 mg pholcodine (as one or two tablets), every hour. Subjects with chronic cough received 10mg pholcodine as two tablets, every 4 hours, but the dosage was increased in most cases as the study progressed. The exact dosage was given depending on severity of cough, and was modified depending on individual response. Acute cough was monitored over a period of a few days and chronic cough over several weeks and up to 7 months. Pholcodine was reported to provide marked or substantial relief in 15 of 19 cases of acute cough (79%) and this was within 12 to 48 hours of drug administration in the majority of the subjects, and in 27 of 35 cases of chronic cough (77%). Of the remaining patients, three with acute and four with chronic cough received no relief, five experienced a slight relief.

Limitations of this study include the fact that it was observational, not controlled or blinded, and it was performed in a heterogeneous population using variable dosages, which makes it difficult to perform comparative efficacy assessments.

### **Mulinos et al (1962)**

This study looked at the efficacy of pholcodine in 23 hospitalized patients (7 female and 16 male) with chronic persistent cough resulting from inflammatory irritation and bronchial secretions associated with pulmonary tuberculosis. Patients received 10 to 20mg of either pholcodine, codeine sulphate, or a placebo, in tablet form, 2 to 4 times per day or every 4 hours. Patients were studied for a period that varied between 1 and 29 days. Frequency of cough, severity, time of day and night and relation with position of the subject, and resultant disturbance of sleep were all recorded. Relief was experienced (reported as 'marked to complete' cough relief) by 100% of patients receiving pholcodine compared to 70% of subjects who received codeine and only 23% of those receiving placebo.

A similar second group of 26 subjects (10 female and 16 male) with tuberculosis were also studied but this time they received the three preparations alternately all within 1 week. The treatments were given only once a day in the evening, and effects such as frequency and severity of cough were recorded in the morning. Patients were asked what their preferred drug was and 67% said they preferred pholcodine. None of the subjects expressed a preference for placebo. In this group 80% of subjects reported relief when given pholcodine, 91% experienced relief with codeine and 51% reported relief from cough after treatment with placebo. Patients slept better following pholcodine and codeine, this was attributed to the alleviation of the cough.

As the physicians recording the efficacy were unaware of which medication had been administered, and the results were collated by a physician who had no contact with the patients, this study can be considered as a blinded study and conducted in a cross over design. No statistical analysis was reported in the article.

While this study was also not conducted or reported in accordance with current standards for demonstration of efficacy, it was an attempt at a blinded placebo-controlled study for which a significant number of patients reported improvement with pholcodine in comparison to placebo.

### **Edwards et al (1977)**

This double-blind, controlled trial measured the effects on frequency of cough in patients with chronic bronchitis. In this study, 24 adult patients (14 male, 10 female,) aged 23 to 70 years (mean age 55 years) were randomised into 4 groups to successively receive on days 2, 3, 4 and 5:

- cough linctus (Pholtex) containing 15 mg pholcodine and 10 mg phenyltoloxamine (a antihistamine) (both attached to ion-exchange resins for slow release);
- one matching treatment containing 15 mg pholcodine alone attached to an ion-exchange resin;
- one matching treatment containing 15 mg pholcodine without resin;
- a placebo syrup base.

Subsequently on each day the patients were given one of four different test preparations prescribed for 24 hours only, a dose of 5 ml at 9.00 hours and 21.00 hours, allocated in random order. Patients were observed for the five consecutive days over the full 24 hours and all coughs were recorded on a tape recorder with a cough activated microphone (Fergfusson model 3248). A count and pattern were established by a scientist blinded to treatment. The treatment-free first day was also monitored and used as control.

The combination regimens (pholcodine and phenyltoloxamine) significantly reduced cough frequency (40-50% reduction) as compared to the control, but pholcodine alone (resinated or not resinated) had a much smaller effect.

### **Rose (1967)**

In this study, the combination of pholcodine 15 mg with pseudoephedrine 60 mg was compared to codeine phosphate 15 mg over a period of one month. The double-blind cross-over trial involved 45 patients (35 men, 10 women) with some degree of chronic respiratory disease. Efficacy evaluation was based on a questionnaire completed by each patient, and a clinician assessment. The pholcodine-containing preparation was effective in relieving cough and breathlessness, and showed superiority to codeine.

As no arm was included in this study containing pholcodine alone, the results do not allow drawing conclusions on the efficacy of pholcodine when administered as a single agent.

### Children

#### **Kelly (1963)**

A report published in 1963 described the results of two studies. One of the studies briefly presented in the paper involved 25 children with acute cough. Complete cough suppression was observed in 19 children, and marked improvement in the remaining 6. Following this pilot study, a larger comparative study was undertaken involving a total of 53 children aged between 8 months and 17 years with acute cough with upper respiratory tract infections. Twenty six of them were given 8 mg/teaspoon oral codeine syrup and the remaining 27 were given 5 mg/teaspoon oral pholcodine syrup (as a proprietary preparation, Ethnine Simplex), at home for 5 days. Patients were allocated to groups on a matching basis for age, diagnosis, nature and duration of cough. Eight patients received both treatments, on a crossover basis. Typical doses were 1 teaspoon 4 times daily for those with productive cough (with a few exceptions of two teaspoonful in very severe cough) and 2 teaspoons 4 times daily for those with unproductive cough (with a few exceptions of only one teaspoonfuls in the very young children).

Parents of the children were asked to keep records of efficacy and side effects. For productive cough the medication was judged as being 'excellent' if cough suppression was almost complete, sufficient to eliminate all disturbance of rest or sleep, 'good' if there was substantial cough suppression meaning much of the disturbance on sleep was reduced; 'fair' when some cough suppression occurred but disturbance in rest and sleep continued and 'poor' where there was no suppression. For unproductive cough the same criteria were used but an excellent classification was only given where complete cough suppression occurred. These records were handed to investigators on visit days which were alternate days during the trial. For both medicines 85% of the patients evaluated had excellent results; 'good' results were reported in 11% of the patients with pholcodine and 8% of the patients with codeine. Within the cross-over group, no significant difference was seen between the two treatments and efficacy was in line with the results obtained in the main group. The duration of effect was greater in the pholcodine group (4h versus 3h).

This study was randomised and can be considered as blinded since both medicines were supplied in the same expedients formulation including banana flavouring agent and parents were unaware of the medicine. It was not placebo controlled and the efficacy criteria could be regarded as subjective and using a mixed rating activity i.e. cough suppression and potentially sedative activity (sleep/disturbance of rest). However, this study can be accepted as showing a positive antitussive effect of pholcodine.

### **Jaffe and Grimshaw (1983)**

A large comparative trial compared efficacy and palatability of two combination products included a total of 217 children between 6 and 12 years old (mean age 8.5 years) suffering from acute cough but in the absence of severe infection. One-hundred and seven (107) patients were randomly given 5 ml Pholcolix 4 times daily (linctus containing pholcodine 5 mg, paracetamol 150 mg, and phenylpropanolamine 12.5 mg, per 5 ml) and 110 were given 7.5 ml Actifed 3 times daily, (linctus containing codeine phosphate 10 mg, triprolidine hydrochloride 1.25 mg, pseudoephedrine hydrochloride 30 mg, per 5 ml) for 3 days. In both groups upper respiratory tract infections predominated, though chest infections were also encountered frequently, and the median duration of symptoms was 3 days with similar patterns of antibiotics.

Efficacy was measured using severity scores from 0 (absent) to 3 (severe) for productive cough, dry cough, sore throat and other cold symptoms. The results showed that both treatments significantly improved productive cough and sore throat. In addition, the Actifed group showed a significant improvement in dry cough whereas the Pholcolix group showed significant improvement in 'other' symptoms, based primarily on headache, earache and catarrh. The results of this study are of difficult interpretation mainly due to the fact that it was performed using combination products.

## **2.3.2. Discussion**

There is 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 is consistent and supportive of the efficacy of pholcodine in the treatment of acute non-productive cough.

The most recent study conducted by Zambon and published in 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 has limitations such as a lack of a placebo control arm and the non-validated and subjective nature of the outcomes (cough frequency and intensity), but an effect was observed very early in the treatment. The results support the efficacy of pholcodine in the treatment of acute non-productive cough.

## **2.4. Risk management plan**

The CHMP did not require the MAHs to submit a risk management plan.

## **2.5. Overall benefit/risk assessment**

### *Safety*

There has been extensive use of pholcodine-containing products over the course of several decades, which has allowed the collection of relevant safety data. The majority of the adverse events reported in clinical trials, literature and post-marketing experience are gastrointestinal disorders and psychiatric disorders, which are adverse events known and commonly reported with opiates. The existent data

seems to indicate that pholcodine is at least as safe as codeine, with the advantage that it does not share the same potential for addiction.

The evidence in support of a link between pholcodine and NMBA-related anaphylaxis derives from ecological studies conducted by a single research team relying on spontaneously reported adverse reactions to NMBAs. While data from Sweden and Norway appear to be consistent, other factors can explain the observations. In recent years the Norwegian network for anaphylaxis under general anaesthesia, which collects these reports, has been subject to less intense promotion, and therefore it is possible that the observed decrease in reporting does not actually reflect lower occurrence. It is also noted that in Norway, although there is a lower number of anaphylaxis reports since pholcodine was withdrawn, the severity of the reactions reported has not changed. Class II and III reactions still represent the majority of the reported cases, same as when pholcodine was still marketed.

The absence of any report of IgE-mediated anaphylactic reaction to NMBAs in Sweden since 1990 raises further questions on the reliability of the data, as regardless of pholcodine use NMBAs would still be expected to cause anaphylactic reactions and the Swedish data does not appear to reflect this expected background rate.

In countries with small populations such as Norway (4.8 million) and Sweden (9.3 million), confounding factors such as a change in anaesthetic procedures, type of products used in anaesthesia and overall use of NMBAs could play a role in explaining the findings.

Even assuming that there is some biological plausibility for the pholcodine-sensitisation and that the spontaneously reported cases reflect the actual prevalence of anaphylactic reactions during surgery, a broad range of other agents may also be responsible. If indeed other substances containing quaternary ammonium ions have the ability to induce cross-sensitisation to NMBAs, and if such substances can be found in numerous household products, the specificity of IgE to pholcodine has to be questioned. This could explain the reason why data from countries such as the USA or the Netherlands does not fit with the pholcodine hypothesis: in these countries pholcodine is not marketed, and still prevalence of IgE to pholcodine and morphine was found to be high. Ultimately, even if the prevalence of sensitisation is high, the clinical relevance of these findings is questionable.

A further issue for consideration is that anaphylactic reactions to pholcodine itself appear to be rare. Very few cases have been described with a substance that has been extensively used for decades and that is even available in some countries without medical prescription.

### *Efficacy*

There is 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 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. Nevertheless, the existing data is consistent and supportive of the efficacy of pholcodine in the treatment of acute non-productive cough.

The most recent study conducted by Zambon and published in 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 has limitations such as a lack of a placebo control arm and the non-validated and subjective nature of the outcomes (cough frequency and intensity), but an effect was observed very early in the treatment. The results support the efficacy of pholcodine in the treatment of acute non-productive cough.

### *Ad-hoc expert group*

An ad-hoc expert group composed mainly of immunologists and anaesthesiologists was consulted to provide advice to CHMP on this issue. The group had split views about the strength of the evidence of an association between pholcodine exposure and allergic reactions to NMBAs, although it was agreed that this is an issue that warrants further investigation.

The majority of the experts considered that although sensitisation to pholcodine and development of allergic reactions to NMBA is a possibility, the existing evidence is weak mainly due to inconsistencies and methodological bias. To support this opinion, some experts referred to the data from the USA showing that there is sensitisation even in the absence of pholcodine consumption, which strengthens the view that other substances are able to trigger this kind of cross-sensitisation. Other experts questioned the specificity of the tests used by the Norwegian research team to detect IgE sensitisation to pholcodine, referred to the lack of a rigorous inclusion criterion for anaphylaxis (ie permitting cases undergoing spontaneous recovery, or a 'mild' presentation) in the investigations, and reference was also made to the use of spontaneously reported adverse events to determine incidence of NMBA-related anaphylaxis. Divergent opinions were expressed on the strength of the epidemiological evidence, based on the Swedish and the Norwegian experiences and the quasi experiment resulting from the discontinuation of the drug in the two countries at different timings and the biological plausibility of the hypothesis.

The experts also considered that the decision to use a NMBA is based on clinical necessity and cannot be avoided, regardless of history of pholcodine use. Therefore investigating pholcodine exposure prior to anaesthesia is currently not done and it would likely be a complicated process, as the majority of patients either will not know or will not remember that they have taken it. In a real-life situation where specialists are unable to take this factor into account in clinical practice, investigation of the pholcodine exposure in individual patients prior to anaesthesia is not considered to be of benefit as it will not change anaesthetic practice.

#### *Conclusions and recommendations*

Taking into account all of the above, the CHMP concluded that the evidence of a link between pholcodine and NMBA-related anaphylaxis is circumstantial, not entirely consistent and does not support the conclusion that there is a significant risk of cross-sensitisation to NMBA and subsequent development of anaphylaxis during surgery. Further data needs to be generated to clarify the possibility of an association between pholcodine use and NMBA-related anaphylaxis.

The Committee therefore concluded that, based on currently available information, the benefits of pholcodine in the treatment of non-productive cough outweigh the risks, and that the benefit-risk balance of pholcodine-containing products in the treatment of non-productive cough is positive under normal conditions of use. The Committee therefore recommended the maintenance of the marketing authorisations for pholcodine-containing products.

Divergent positions are presented in Appendix 1.

Nevertheless the CHMP considered that the possibility of an association between pholcodine and NMBA-related anaphylaxis needs to be further investigated. To this end, Marketing Authorisation Holders shall, within 3 months of the Commission Decision, submit for assessment and approval the protocol of a case-control study.

Due to the low incidence of NMBA-related anaphylaxis reactions and the fact that currently pholcodine is only marketed in a limited number of European countries, the Committee strongly recommends that in order to fulfil this commitment MAHs collaborate with groups/networks like the Groupe d'Études des Réactions Anaphylactiques Peranesthésiques (GERAP), who has been working with the rapporteur on a protocol for such a case-control study. The draft synopsis of this protocol currently foresees that cases should be defined as patients who experienced an anaphylactic reaction immediately at induction of anaesthesia using any NMBA, and controls as patients who underwent anaesthesia using one NMBA but did not experience any anaphylactic or anaphylactoid reaction. Each case should be matched with at least 2 controls, based on appropriate criteria such as age groups, gender, NMBA and time of anaphylactic reaction. A minimum of 165 cases and 330 controls are expected to be needed to ensure statistical power. Assessment of exposure to pholcodine should include a questionnaire on use in the 6 previous months, including visual aids to identify specific products. The investigation of cases and controls should include specific IgE and skin tests.

A multicentric study conducted in France (one of the few European countries where exposure to pholcodine and number of NMBA-related anaphylaxis cases appears to be significant enough to allow investigation) would be expected to detect up to 100 cases per year. Based on this assumption, the estimated study duration would be 3 years.

Considering that as a part of this procedure:

- The CHMP already assessed the evidence available to date from across the Member States on this topic, and during the assessment has been able to identify its shortcomings
- The preliminary proposals for the study protocol submitted by different MAHs have already been reviewed by the CHMP during this referral procedure

The Committee considers it important to coordinate the review of the protocol of the case-control study to ensure the studies are suited to generate the data required to assess the possible association between pholcodine use and NMBA-related anaphylactic reactions.

### **3. Overall conclusion**

The Committee reviewed the available data on the safety and efficacy of pholcodine, particularly the data in support of a link between pholcodine use and development of NMBA-related anaphylaxis.

The Committee considered that evidence of an association between pholcodine use and development of NMBA-related anaphylaxis is circumstantial, not entirely consistent and therefore does not support the conclusion that there is a significant risk of cross-sensitisation to NMBAs and subsequent development of anaphylaxis during surgery.

The Committee also considered that data from clinical trials and extensive post marketing use has demonstrated the efficacy of pholcodine in the treatment of non productive cough.

The Committee therefore concluded that, based on currently available data, the benefit-risk balance of pholcodine-containing products in the treatment of non-productive cough is positive under normal conditions of use.

The Committee recommended the maintenance of the marketing authorisations for the medicinal products referred to in Annex I of the opinion. The Committee also concluded that further investigation on the possibility of an association between pholcodine use and NMBA-related anaphylaxis is needed, and to that end MAHs shall conduct a case-control study.

**Appendix 1:**

***Divergent positions***

Procedure No: EMEA/H/A-31/1292

The undersigned members of CHMP did not agree with the Committee's opinion recommending the maintenance of the marketing authorisations for pholcodine-containing products. The reasons for divergent opinion were the following:

Previous exposure to pholcodine has been suspected to be one of the factors triggering anaphylactic reactions following administration of Neuro Muscular Blocking Agents (NMBA). This hypothesis is mainly based on the observation that such reactions were greatly reduced in Norway and Sweden after withdrawal of pholcodine-containing products from the market.

Due to the severity of anaphylactic reactions (some of them being fatal) and due to the absolute need for NMBA use in anaesthetic procedures, more information appears clearly needed to further investigate relationships between such reactions and pholcodine exposure. The most effective way of performing these investigations would be to renew the Scandinavian experience by following up the incidence of anaphylactic reactions after withdrawal of pholcodine-containing products in other countries, instead of performing a case control study which requires that pholcodine remains on the market until results of the study become available.

Alternative treatments are available for non-productive cough and maintenance of these drugs in Norway and Sweden did not prevent the decrease of anaphylactic reactions to NMBA. This fact makes unlikely the involvement, in NMBA-related anaphylactic reactions, of other compounds containing quaternary ammonium within their chemical structure, such as codeine.

Pierre Demolis	15 December 2011	Signature:
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