

## **Annex II**

**Scientific conclusions and grounds for the maintenance of the marketing authorisations presented by the EMA**

## Scientific conclusions

### Overall summary of the scientific evaluation of pholcodine-containing products (see Annex I)

#### *Background information*

Pholcodine is an opiate with central antitussive action used for treatment of cough and cold symptoms in children and adults. The first clinical studies on efficacy of pholcodine as an antitussive agent are dated 1950. Pholcodine has been marketed for decades in the European Union, where currently marketing authorisations exist in Belgium, France, Ireland, Lithuania, Luxembourg, Malta, Slovenia, Spain and United Kingdom, either subject to medical prescription or as non-prescription medicines.

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for medicinal products containing pholcodine-containing medicinal products should be maintained, varied, suspended or withdrawn.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 concerns of the French Medicines Agency 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.

#### *Scientific discussion*

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.

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<sup>1,2</sup>. 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>3</sup>.

The evidence in support of this 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 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

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<sup>1</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>2</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.

<sup>3</sup> Johansson SGO et al. Pholcodine caused anaphylaxis in Sweden 30 years ago. *Allergy* 2009; 64: 820-821.

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.

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 NMBAs 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 need 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.

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.

#### *Conclusion 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 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.

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 authorisation for pholcodine-containing products.

Nevertheless the Committee considered that the possibility of an association between pholcodine use and NMBA-related anaphylaxis needs to be further investigated. For this purpose, Marketing Authorisation Holders shall conduct a case-control study as described in annex III of this opinion. The draft protocol of the study should be submitted to CHMP within 3 months of the Commission Decision.

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.

## **Grounds for the maintenance of the marketing authorisations**

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 information, 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.

The conditions affecting the marketing authorisations are set out in Annex III.