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Questions and answers on the review of the marketing authorisations for medicines containing pholcodine

Outcome of a procedure under Article 31 of Directive 2001/83/EC as amended

The European Medicines Agency has completed a review of the safety and effectiveness of pholcodine, following concerns that its use may put people at risk of developing anaphylactic (severe allergic) reactions to neuromuscular blocking agents used during surgery. The Agency's Committee for Medicinal Products for Human Use (CHMP) has concluded that the existing evidence of the risk is weak, and that the benefits of pholcodine continue to outweigh its risks. Therefore, it recommended that all marketing authorisations for medicines containing pholcodine should be maintained throughout the European Union (EU).

What is pholcodine?

Pholcodine is an opioid medicine that is used for the treatment of non-productive (dry) cough in children and adults. It works directly in the brain, depressing the cough reflex by reducing the nerve signals that are sent to the muscles involved in coughing.

Pholcodine has been used as a cough suppressant since the 1950s. Pholcodine-containing medicines are currently approved in the EU in Belgium, France, Ireland, Lithuania, Luxembourg, Malta, Slovenia, Spain and the United Kingdom, either subject to medical prescription or as over-the-counter medicines. They may be available as syrups, oral solutions, suppositories, tablets and capsules under various trade names and as generics.

Why was pholcodine reviewed?

At the time of the review, pholcodine-containing medicines had been withdrawn from the markets in Sweden (in the 1980s) and Norway (in 2007). In 2009, a study was published indicating that the reduction in pholcodine consumption in these countries was associated with a decrease in reports of anaphylactic reactions to neuromuscular blocking agents (NMBAs). NMBAs are used in emergency hospital procedures to prevent spontaneous muscle movements during surgery. Further publications in 2010 and 2011 from the same authors supported the hypothesis that pholcodine use may increase the likelihood of patients having an anaphylactic reaction if they are exposed to an NMBA. In France, data

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from spontaneous reports also suggested a 25% increase in anaphylactic reactions to NMBAs coinciding with a 9% increase in pholcodine use.

Consequently, the French medicines regulatory agency changed the prescription status for these medicines in France from over-the-counter to prescription-only, and asked the CHMP to carry out a full assessment of the benefit-risk balance of pholcodine and to issue an opinion on whether the marketing authorisations for pholcodine-containing products should be maintained, varied, suspended or withdrawn across the EU.

Which data has the CHMP reviewed?

The CHMP reviewed all the available data on the effects of pholcodine as a cough suppressant. To assess its safety, the Committee reviewed the results from preclinical and clinical studies, post-marketing data, epidemiological studies and data from the published literature. A group of experts in immunology and anaesthesia was also convened to provide advice.

What are the conclusions of the CHMP?

Regarding pholcodine's benefits, the CHMP noted that there is a large body of data demonstrating the effectiveness of opioids in the management of non-productive cough and that pholcodine has been in use for several decades. Regarding pholcodine's safety, the majority of adverse effects reported with pholcodine are those commonly seen with opioid medicines.

The hypothesis that pholcodine use could trigger anaphylactic reactions to NMBAs is based on the body producing antibodies against pholcodine, which eventually trigger reactions to NMBAs ('cross-sensitisation'). The CHMP considered that, although this is biologically plausible, the available data are weak and not fully consistent. The Committee noted that the study in Sweden and Norway looked at changes in reporting rates of adverse reactions to NMBAs following the withdrawal of these medicines, without convincingly establishing a causal link with pholcodine use. Cross-sensitisation has also been observed in countries where pholcodine is not on the market, suggesting that other substances may also trigger cross-sensitisation and that the observed changes in reporting rates may be explained by other factors. Therefore, the CHMP concluded that the existing evidence does not support the conclusion that the use of pholcodine-containing medicines presents a risk of developing anaphylactic reactions to NMBAs. The Committee nevertheless recommended that a new post-marketing study investigating the possibility of an association between pholcodine and anaphylactic reactions to NMBAs should be carried out.

Based on the evaluation of the currently available data and the scientific discussion within the Committee, the CHMP concluded that the benefits of pholcodine-containing medicines continue to outweigh their risks, and therefore recommended that all marketing authorisations for these medicines should be maintained.

What are the recommendations for patients and healthcare professionals?

- Patients and healthcare professionals are reminded that the benefits of pholcodine continue to outweigh its risks for the treatment of non-productive cough. No new risks have been identified with pholcodine.
- Patients taking pholcodine-containing medicines can continue to do so, and should contact their doctor or pharmacist if they have any questions about their treatment.

The European Commission issued a decision on 17 February 2012.