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Review of pholcodine medicines started

The European Medicines Agency (EMA) has started a review of medicines that contain pholcodine following concerns that their use may put people at risk of developing anaphylactic reactions (a sudden, severe and life-threatening allergic reaction) to certain medicines called neuromuscular blocking agents (NMBA). Pholcodine is used to treat non-productive (dry) cough in adults and children and NMBAs are used in general anaesthesia to prevent spontaneous muscle movements to improve operating conditions.

The review was requested by the French medicines agency (ANSM) following preliminary results of a study (ALPHO) carried out in France[1]. The results of the study suggested that taking pholcodine up to 12 months before general anaesthesia may increase the risk of having an NMBA-related anaphylactic reaction. Based on these results ANSM is considering, as a precautionary measure, to suspend the use of pholcodine-containing medicines in France.

The ALPHO study was carried out as a condition to the marketing authorisations of pholcodine-containing medicines following a previous safety review in 2011. At the time, the Agency's Committee for Medicinal Products for Human Use (CHMP) found no firm evidence that use of pholcodine may put people at risk of developing anaphylactic reactions to NMBAs and recommended that a new study (the ALPHO study) should be carried out to investigate this risk in people taking pholcodine.

While ALPHO study was ongoing, in 2021, a study in Australia[2] linked pholcodine's use to an increased risk of anaphylaxis to NMBA muscle relaxants. This led to a recommendation by PRAC to include relevant warnings in the product information of pholcodine-containing medicines.

The PRAC will now review the results of the ALPHO study together with all available data and assess their impact on the benefit-risk balance of pholcodine-containing medicines and issue a recommendation on whether their marketing authorisations should be maintained, varied, suspended or withdrawn across the EU.

The Agency invites all stakeholders (e.g. healthcare professionals, patients' organisations, the general public) to submit data relevant to this procedure. Full details are available in the Stakeholder's submission form.

[1] Allergy to Neuromuscular Blocking Agents and Pholcodine Exposure (ALPHO) https://clinicaltrials.gov/ct2/show/NCT02250729

[2] Sadleir et al. Relationship of perioperative anaphylaxis to neuromuscular blocking agents, obesity, and pholcodine consumption: a case-control study. Br J Anaesth (2021) May;126(5):940-948. doi: 10.1016/j.bja.2020.12.018. Epub 2021 Jan 14. https://pubmed.ncbi.nlm.nih.gov/33454050/

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More about the medicine

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. In the EU pholcodine-containing medicines are currently approved in Belgium, Croatia, France, Ireland, Lithuania, Luxembourg and Slovenia, either subject to medical prescription or as over-the-counter medicines. They often contain pholcodine in combination with other substances and are available as syrups, oral solutions, and capsules under various trade names and as generics. Pholcodine is marketed under various names including Dimetane, Biocalyptol and Broncalene.

More about the procedure

The review of pholcodine has been initiated at the request of France, under Article 107i of Directive 2001/83/EC.

The review is being carried out by the Pharmacovigilance Risk Assessment Committee (PRAC), the Committee responsible for the evaluation of safety issues for human medicines, which will make a set of recommendations. As pholcodine-containing medicines are all authorised nationally in some Member States, the PRAC recommendations will be forwarded to the Co-ordination Group for Mutual Recognition and Decentralised Procedures – Human (CMDh), which will adopt a position. The CMDh is a body representing EU Member States as well as Iceland, Liechtenstein and Norway. It is responsible for ensuring harmonised safety standards for medicines authorised via national procedures across the EU.