NOTIFICATION TO THE PRAC/EMA SECRETARIAT OF A REFERRAL UNDER ARTICLE 107i OF DIRECTIVE 2001/83/EC
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This notification is a referral under Article 107i of Directive 2001/83/EC to the PRAC made by France (ANSM):

Product Name(s) in the Referring Member State, if applicable	DIMETANE SANS SUCRE 133 mg/100 ml, sirop BIOCALYPTOL 6,55 mg/5 ml SANS SUCRE, sirop édulcoré à la saccharine sodique et au maltitol liquide BIOCALYPTOL A LA PHOLCODINE, sirop BIOCALYPTOL, sirop BRONCALENE ADULTES, sirop BRONCALENE ENFANTS, sirop PHOLCODINE BIOGARAN 6,55 mg/5 mL, sirop
Active Substance(s)	Pholcodine
Pharmaceutical form(s)	All
Strength(s)	All
Route(s) of Administration	All
Marketing Authorisation Holder(s) in the Referring Member State	BIOCODEX, BIOGARAN, MELISANA PHARMA, ZAMBON FRANCE

Background

Pholcodine (3-morpholinoethylmorphine), a semi-synthetic alkaloid, is a cough suppressant that acts primarily on the central nervous system causing depression of the cough reflex, partly by a direct effect on the cough centre in the medulla. It is used alone and in combination with other active substances (e.g. biclotymol, chlorphenamine maleate) in preparations to treat the symptoms of common cold. Pholcodine is currently authorised in seven Member States (FR, LT, IE, HR, SI, BE, LU).

In 2011, an article 31 referral was initiated by the French National Agency for Medicines and Health Products (ANSM) concerning a potential risk of IgE-sensitisation to neuromuscular blocking agents (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 the available data during the referral procedure, the Committee for Medicinal Products for Human Use (CHMP) established that the evidence of a link between pholcodine and NMBA-related anaphylaxis was circumstantial, not entirely consistent and did not support the conclusion that there was a significant risk of cross-

sensitisation to NMBAs and subsequent development of anaphylaxis during surgery. The CHMP therefore concluded that, based on currently available information, the benefit-risk balance of pholcodine-containing products in the treatment of non-productive cough was positive under normal conditions of use and recommended the maintenance of the marketing authorisations. 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 as a condition of the marketing authorisations of pholcodine-containing products (European Commission decision (2012)1172[1]). As a result, a multicentric case-control study (ALPHO study), including 24 centers, was conducted in France only. Enrolment started in 2014 and finished in July 2020 but the results were not available in 2021 due to accumulated delays including slow recruitment rates over the years and later the coronavirus disease (COVID-19) pandemic.

Meanwhile, in 2021, an Australian team (Sadleir *et al.*[2]) 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 with respect to BMI grade, history of pholcodine consumption, sex, age, comorbid disease, and NMBA type and dose. Patients were included prospectively and retrospectively, and collection of data of pholcodine consumption were carried out retrospectively, several years earlier for some patients leading to a potential increased risk of memory bias. 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 (adjusted OR =12.7, 95% CI [3.8 – 43.1], p <0.001). This study was assessed during the Periodic Safety Update Report single assessment (PSUSA) procedure of pholcodine finalised in 2022 (PSUSA/00002396/202105)[3]. As an outcome, notwithstanding the different anaesthesia practices and thus the fact that the results from the Australian study cannot 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 to update the product information of all pholcodine-containing products (including fixed dose combinations), while waiting for the results of the ALPHO study, to warn patients and healthcare professionals that cross-reactivity leading to serious allergic reactions (anaphylaxis) have been reported between pholcodine and NMBAs. The Co-ordination Group for Mutual Recognition and Decentralised procedures - Human (CMDh) agreed on this variation of the marketing authorisations based on the PRAC recommendation and in addition, requested the MAHs involved in the ALPHO study to provide results of the study as soon as possible and no later than 30th June 2022 (CMDh meetings on 25-27 January 2022 and on 21-22 June 2022).

Issues to be considered

On 30th June 2022, the ANSM received a preliminary study report of the PASS ALPHO from the sponsor (Nancy University hospital) providing the results of the analysis on the primary endpoint. No further analyses for primary endpoint are expected to be presented in the final report.

The primary objective of this case-control study was to investigate an association between pholcodine exposure and the risk of perianaesthetic NMBA-related anaphylactic reaction by comparing a group of patients who experienced a anaphylactic reaction at anaesthetic induction 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 study included a total of 937 patients for 167 cases and 334 controls. The results on the primary endpoint of the study showed a statistically significant link between exposure to pholcodine during the 12 months preceding surgery and a risk of perianaesthetic anaphylactic reaction related to NMBA after adjusting for potential confounding factors (adjusted OR = 4.4, 95% CI [2.6; 7.3] $p < 10^{-4}$).

Based on these new data which are consistent with the Australian study from Sadleir *et al*, the ANSM considers the hypothesis that pholcodine consumption is likely associated with an increased risk of unpredictable perianaesthetic NMBA-related anaphylactic reaction, as confirmed.
The ALPHO study was imposed after the 2011 referral specifically to investigate the possibility of an association between pholcodine use and NMBA-related anaphylactic, and provides more robust results for the EU than the Australian study as per the methodology (multicentric study conducted in the EU in a significant number of patients).

The final report of ALPHO study, including data for the secondary objectives (focusing on the mechanism of action of the anaphylactic reaction, the role of anti-pholcodine IgE), should be available mid-September 2022 and is not expected to have an impact on the results and conclusions of the preliminary report. Considering the importance of the risk that is evidenced from ALPHO, the fact that these results concur with the results of the Australian study, and considering the symptomatic indication, the ANSM considers that measures to protect the population should be taken without delays.

In light of these new data on the primary outcome of the ALPHO study (collected from a large number of patients in a European multicentric study imposed as a condition of the marketing authorisations) showing a statistically significant link between exposure to pholcodine and the risk of perianaesthetic anaphylactic reaction related to NMBA, and taking into account the seriousness and the unpredictability of this risk (e.g. use of NMBAs in an emergency context) and that pholcodine is used to treat non-life-threatening functional symptoms (non-productive cough), the ANSM is of the view that the benefit-risk ratio for pholcodine-containing products is no longer considered favourable and considers suspending the corresponding marketing authorisations in France.

In view of the above, France initiates an urgent union procedure under Article 107i of Directive 2001/83/EC and refers the matter to the PRAC which is requested to give its recommendation as to whether marketing authorisations of these products should be maintained, varied, suspended, or revoked.

As the request results from the evaluation of data resulting from pharmacovigilance activities, the opinion should be adopted by the CMDh on the basis of a recommendation of the PRAC.

Signed Date

CAROLINE SEMAILLE ID

Signature numérique de CAROLINE SEMAILLE ID
Date : 2022.08.19 16:41:46 +02'00'

References:
1. European Commission decision (2012)1172, https://ec.europa.eu/health/documents/community-register/html/ho22581.htm
2. Sadleir PHM, Clarke RC, Goddard CE, Day C, Weightman W, Middleditch A, Platt PR. 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.
3. Pholcodine: CMDh scientific conclusions and grounds for the variation, amendments to the product information and timetable for the implementation - PSUSA00002396202105 (europa.eu). https://www.ema.europa.eu/en/documents/psusa/pholcodine-cmdh-scientific-conclusions-grounds-variation-amendments-product-information-timetable/00002396/202105_en.pdf