Annex II

Scientific conclusions

Scientific conclusions

Pholcodine is a morphinane alkaloid that is a derivative of morphine with a 2-morpholinoethyl group at the 3-position. It is an opiate acting directly on the medulla oblongata, cough centre of the central nervous system (CNS) used for treatment of cough and cold symptoms in children and adults.

Pholcodine has been used as a cough suppressant since the 1950s. In the European Union (EU), pholcodine-containing medicines are currently approved in seven EU Member states (MSs): Belgium, Croatia, France, Ireland, Lithuania, Luxembourg and Slovenia. Pholcodine-containing products are also available in Northern Ireland. Pholcodine-containing products are marketed in the EU MSs for symptomatic treatment of acute dry, non-productive cough in adults and children. Age limit for use in children varies between the authorised products with 30 months being the lowest age limit authorised. Pholcodine-containing medicinal products are available both with and without medical prescription. The products available without medical prescription have limited duration of use up to several days after which medical advice should be sought which is in line with general guidance for over-the-counter (OTC) products. A rough estimate of the cumulative exposure for all products in all EU countries combined is approximately 1 025 437 089 patient-years. The exposure is the highest in France, where the cumulative exposure is approximately 1 022 141 456 patient-years.

In 2011, an article 31 referral was initiated by the 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 available data during the referral procedure in 2011, the Committee for Medicinal Products for Human Use (CHMP) established that the evidence of a link between pholcodine use and NMBA-related anaphylaxis was circumstantial, not entirely consistent and not supportive of a conclusion that there was a significant risk of cross-sensitisation to NMBAs and subsequent development of anaphylaxis during surgery. 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.

Meanwhile, in 2021, an Australian team (Sadleir et al. 2021) 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. 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. This study was assessed during the Periodic Safety Update Report single assessment (PSUSA) procedure of pholcodine finalised in 2022 (PSUSA/00002396/202105). As an outcome, notwithstanding the different anaesthesia practices and thus the fact that the results from the Australian study could not 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, while waiting for the results of the ALPHO study, to update the product information of all pholcodine-containing products (including fixed

dose combinations) to warn patients and healthcare professionals (HCPs) that cross-reactivity leading to serious allergic reactions (anaphylaxis) have been reported between pholcodine and NMBAs.

The preliminary results of the ALPHO study, the imposed post-authorisation safety study (PASS) assessing the risk of anaphylaxis to NMBAs after use of pholcodine conducted as a condition of the marketing authorisations of pholcodine-containing medicinal products following the previous referral in 2011 were received by French medicines agency (ANSM) on 30 June 2022. The study results showed a statistically significant link between exposure to pholcodine and the risk of perianaesthetic anaphylactic reaction related to NMBAs.

Based on these new data which are consistent with the Australian study from Sadleir et al, the ANSM considered the hypothesis that pholcodine consumption is likely associated with a risk of unpredictable perianesthetic NMBA-related anaphylactic reaction, as confirmed. Even if the Australian study has shown that pholcodine consumption could be a risk factor of NMBA anaphylaxis, the results of this monocentric study could not be fully extrapolated to the EU due to different anaesthesia practices. The ALPHO study was imposed after the 2011 referral as a condition of the marketing authorisation for the EU, and provided more robust results as per the methodology (multicentric study conducted in the EU in a significant number of patients).

In light of the new data from the PASS, taking into account the seriousness and the unpredictability of this risk and that pholcodine-containing medicinal products is used to treat non-life-threatening functional symptoms (non-productive cough), the ANSM was of the view that the benefit-risk ratio of pholcodine-containing medicinal products was no longer favourable and considered suspending the marketing authorisations of these products in France.

On 19 August 2022 the French medicines agency (ANSM) triggered an urgent Union procedure under Article 107i of Directive 2001/83/EC, and asked the PRAC to assess the impact of the above concerns on the benefit-risk balance of pholcodine-containing medicinal products and issue a recommendation on whether the marketing authorisation(s) of these products should be maintained, varied, suspended or revoked.

The PRAC adopted a recommendation on 01 December 2022 which was then considered by the CMDh, in accordance with Article 107k of Directive 2001/83/EC.

Overall summary of the scientific evaluation by the PRAC

The totality of available data suggests that the efficacy of pholcodine-containing medicinal products in symptomatic treatment of non-productive cough is considered established considering the marketing authorisations for these medicinal products as well as the conclusions on efficacy in the previous CHMP referral in 2011. No new efficacy data became available since the previously mentioned referral. In terms of the overall safety profile of pholcodine, the majority of adverse drug reactions belong to gastrointestinal and psychiatric disorders, similarly as for other opioids. However, throughout the years, case reports and results from studies raised the concern that patients treated with pholcodine 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.

Concerning this risk, in 2011, the CHMP conducted a review and considered that the evidence of a link between pholcodine and NMBA-related anaphylaxis was circumstantial and not entirely consistent. CHMP, nevertheless, concluded that further investigation on the possibility of an association between pholcodine use and NMBA-related anaphylaxis was needed. As an outcome of the referral, the conduct of a PASS (post-authorisation safety study) was imposed. The results of such study, named ALPHO, became available in 2022 and were thoroughly assessed in the present safety review. The results from the ALPHO study showed a statistically significant link between use of pholcodine during the 12 months preceding anaesthesia and risk of perianesthetic anaphylactic reaction related to NMBAs (OR

adjusted=4.2 CI 95% [2.5; 6.9]). Despite some identified study limitations, the data from this study show an association between the risk of NMBA-related anaphylaxis and previous pholcodine use that cannot be refuted by other effects or biases. Moreover, the findings of the ALPHO study add to the cumulating evidence from literature reports and previous epidemiological studies that pholcodine is an important risk factor for NMBA-related anaphylaxis. Therefore, PRAC is of the view that based on the totality of evidence a causal relationship between pholcodine use and NMBA-related anaphylaxis is considered sufficiently established.

It should be also highlighted, that despite the low number of documented cases of anaphylaxis specifically against pholcodine, perioperative anaphylaxis (including anaphylaxis to NMBAs) is a serious and life threatening medical condition which is rare (1/10.000 anaesthesia procedures) but with relatively high mortality (4-6%). Therefore, all available measures should be taken to decrease its incidence. As discussed in section 2.2.4, it is noted that a broader range of agents can induce cross-sensitization to NMBAs and cause NMBA-related anaphylaxis. In the ALPHO study, exposure to such agents was a confounding risk. The exposure to these agents, such as occupational exposure to quaternary ammonium ions for example, however may not be possible to identify nor to fully prevent or minimise. Based on the evidence reviewed, pholcodine is identified as a risk factor for NMBA-related anaphylaxis regardless of other risk factors. Importantly, epidemiological studies indicate that numbers of perioperative anaphylaxis cases are significantly reduced after pholcodine-containing medicinal products were removed from the market. This is supported by a study conducted in Norway, when six years after withdrawal of pholcodine-containing medicinal products from the Norwegian market, the Norwegian population became significantly less IgE sensitized and clinically more tolerant to NMBAs (De Pater, 2017). These results indicate the possible impact of acting upon the pholcodine usage.

In the context of the procedure and facing the evidence reviewed and noted above, PRAC discussed potential measures which would minimise the risk of NMBA-related anaphylaxis to an acceptable level such as restriction of indication, PI updates, change to prescription-only status, patient alert card and dissemination of Direct Healthcare Professional Communication (DHPC). Overall, the risk minimisation measures (RMMs) are not considered by PRAC appropriate and effective measures to reduce the risk NMBA-related anaphylaxis in patients previously treated with pholcodine to an acceptable level. In general, the RMMs discussed would increase HCPs and patient awareness of the existing risk (e.g., SmPC changes, DHPC, patient alert card) or would reduce the number of the patients using pholcodine (e.g., restriction of indication or change of legal status). However, these measures would not minimize the risk of NMBA-related anaphylaxis for individual patient exposed to pholcodine. Moreover, the decision to use a NMBA during anaesthesia is based on clinical necessity and cannot be avoided in any subpopulation, regardless of history of pholcodine use. Therefore, patients exposed to pholcodine would still be at risk of NMBA-related anaphylaxis, which is regarded as serious, unpredictable and life threatening. PRAC could also not identify measures that would allow HCPs to identify which patients treated with pholcodine will develop cross-sensitization and reactions to NMBAs. Further, the PRAC could not identify condition(s) which if fulfilled would demonstrate a positive benefit-risk balance for these products in a defined patient population. Lastly, PRAC noted that other therapeutic alternatives for treatment of non-productive dry cough are available in the EU MS, such as codeine, ethylmorphine, dextromethorphan, butamirate and others.

Therefore, the PRAC concluded that the risk of perianaesthetic anaphylactic reaction related to NMBAs outweighs the benefits of pholcodine-containing medicinal products in treatment of non-productive cough, a symptomatic indication considered acute and not serious.

Consequently, the PRAC recommended the revocation of the marketing authorisations for pholcodine-containing medicinal products.

Grounds for PRAC recommendation

Whereas,

- The PRAC considered the procedure under Article 107i of Directive 2001/83/EC for pholcodine-containing medicinal products.
- The PRAC reviewed the totality of the data available for pholcodine-containing medicinal products in relation to the risk of perianaesthetic anaphylactic reaction related to NMBAs, in writing and in an oral explanation. This included the results of observational studies (including the ALPHO study), literature data, post-marketing case reports as well as responses submitted by the MAHs and the submissions by the stakeholders.
- The PRAC considered that the data reviewed confirm an association between the use of pholcodine and the risk of perianaesthetic anaphylactic reaction to NMBAs, an unpredictable and potentially life-threatening situation.
- No specific characteristics for perianesthetic anaphylactic reaction to NMBA could be identified in patients who have been treated with pholcodine, and therefore all these patients are considered at risk. In addition, the PRAC could not identify risk minimisation measures that would be effective at reducing the risk of perianaesthetic anaphylactic reaction related to NMBAs in patients who have been treated with pholcodine-containing medicinal products.
- The PRAC therefore concluded that the risk of perianaesthetic anaphylactic reaction related to NMBAs outweighs the benefit of pholcodine in the treatment of non-productive cough, a symptomatic indication considered acute and not serious.
- Further, the PRAC could not identify conditions which if fulfilled would demonstrate a positive benefit-risk balance for pholcodine-containing medicinal products in a defined patient population.

In view of the above, the PRAC concluded that the benefit-risk balance of pholcodine-containing medicinal products is no longer favourable and should be revoked.

CMDh position

Having reviewed the PRAC recommendation, the CMDh agrees with the PRAC overall conclusions and grounds for recommendation.

Overall conclusion

The CMDh, as a consequence, considers that the benefit-risk balance of pholcodine-containing medicinal products is not favourable.

Therefore, pursuant to Article 116 of Directive 2001/83/EC, the CMDh recommends the revocation of the marketing authorisations for pholcodine-containing medicinal products.