Annex I

Scientific conclusions and grounds for the variation to the terms of the Marketing Authorisation(s)

Scientific conclusions

Taking into account the PRAC Assessment Report on the PSUR(s) for pholcodine, the scientific conclusions are as follows:

Cumulatively 9 cases of misuse including 7 fatal overdoses were identified. The circumstances of the intoxication of pholcodine were not reported and a potential abuse or dependence with pholcodine cannot be firmly established. However, medical history of substance abuse with use of concomitant opioids in several cases of fatal overdose may suggest a potential abuse of pholcodine in these patients. In addition, in two cases reported from a published article, pholcodine concentrations in the hair seem to indicate repeated and escalating use of pholcodine during the months preceding death in these cases, which could reflect abuse of pholcodine. In view of available data on drug abuse from the literature and spontaneous reports, the PRAC considers a causal relationship between pholcodine and drug abuse cannot be ruled out. The PRAC concluded that the product information of products containing pholcodine should be amended accordingly.

In view of available data on risk(s) of IgE sensitisation and subsequent cross-sensitivity to Neuromuscular Blocking Agents (NMBAs) from the literature, the PRAC considers a causal relationship between pholcodine and cross-reactivity to NMBAs cannot be ruled out. The PRAC concluded that the product information of products containing pholcodine should be amended accordingly

The CMDh agrees with the scientific conclusions made by the PRAC.

Grounds for the variation to the terms of the Marketing Authorisation(s)

On the basis of the scientific conclusions for pholcodine the CMDh is of the opinion that the benefit-risk balance of the medicinal product(s) containing pholcodine is unchanged subject to the proposed changes to the product information.

The CMDh reaches the position that the marketing authorisation(s) of products in the scope of this single PSUR assessment should be varied. To the extent that additional medicinal products containing pholcodine are currently authorised in the EU or are subject to future authorisation procedures in the EU, the CMDh recommends that the concerned Member States and applicant/marketing authorisation holders take due consideration of this CMDh position.

Annex II

Amendments to the product information of the nationally authorised medicinal product(s)

Amendments to be included in the relevant sections of the Product Information (new text **underlined and in bold**, deleted text ~~strike through~~)

Summary of Product Characteristics

Section 4.4

A warning should be added as follows:

Caution is needed in patients with a history of drug abuse. Pholcodine is an opioid and addiction is observed with opioids as a class.

A warning should be added as follows:

Cross-reactivity leading to serious allergic reactions (anaphylaxis) have been reported between pholcodine and NMBAs (Neuromuscular Blocking Agents). A precise at-risk period of time between the exposures of pholcodine and NMBAs has not been determined. Clinicians should be aware of this potential in case of future anaesthetic procedures involving NMBAs.

Package Leaflet

2. What you need to know before you take pholcodine

Consult a doctor before use if you have a history of drug abuse; pholcodine is an opioid and addiction is observed with opioids as a class.

Cases of cross-reactivity with medicines called muscle relaxants used during anaesthesia, resulting in serious allergic reactions (anaphylaxis) have been reported in patients who have previously taken pholcodine. If are due to undergo anaesthesia at any time (such as for surgery), please inform your anaesthetist that you have taken pholcodine in the past.

Annex III

Timetable for the implementation of this position

Timetable for the implementation of this position

Adoption of CMDh position:	January 2022 CMDh meeting
Transmission to National Competent Authorities of the translations of the annexes to the position:	13 March 2022
Implementation of the position by the Member States (submission of the variation by the Marketing Authorisation Holder):	12 May 2022