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:

Cumulative data of Acute Generalised Exanthematous Pustulosis (AGEP) with pholcodine were reviewed. A total of 14 cases of AGEP have been identified cumulatively from post-marketing experience with pholcodine.

Co-suspected drug known to induce AGEP was reported in four cases but in the majority of cases no other reported drug concomitantly administered or drug not known to induce severe cutaneous reactions were reported. In two cases with concomitant treatments, the chronology reported was more suggestive for pholcodine than for suspected treatments and the causality of pholcodine appears more plausible than for the co-suspected drugs. In addition, in six cases pholcodine was the only suspected drug. AGEP is attributed to drugs in more than 90% of cases and in some cases reported pholcodine seems to be the most plausible cause of the occurrence of AGEP. Positive dechallenge was reported in the great majority of cases, including five cases where pholcodine was the only suspected drug. Finally, in one case allergic tests performed was positive for pholcodine containing product and negative for the co-suspected drug.

Taking into account the patient exposure, the PRAC concluded that there is a reasonable causal relationship between pholcodine and the occurrence of AGEP and that a change in the product information is warranted to inform prescribers and patients and to allow early discontinuation of the treatment in case of occurrence of AGEP.

Based on the review of the post-marketing data, the PRAC recommends the update of section 4.4 and 4.8 of the SmPC to add the adverse reaction Acute Generalised Exanthematous Pustulosis with a frequency unknown. The Package leaflet is updated 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:

Severe cutaneous adverse reactions (SCARs) including acute generalized exanthematous pustulosis (AGEP), which can be life-threatening or fatal, have been reported in patients treated with <medicine>, most likely in the first week. Patients should be advised of the signs and symptoms and monitored closely for skin reactions. If signs and symptoms suggestive of these reactions appear, <medicine> should be withdrawn immediately.

- Section 4.8

The following adverse reaction(s) should be added under the SOC Skin and subcutaneous tissue disorders with a frequency unknown:

Acute generalized exanthematous pustulosis (see section 4.4)

Package Leaflet

- Section 2 :

Do not take this <medicine>:

If you have ever developed a severe skin rash or skin that peels, blisters and / or sores in the mouth after taking <drug> or other <related drug>

Warnings and precautions:

Serious skin reactions, including acute generalized exanthematous pustulosis (AGEP), have been reported with the use of <medicine>. AGEP is a generalized, red, scaly rash with bumps under the skin and vesicles associated with fever. Most common location: mainly located on the folds of the skin, the trunk and the upper limbs. The highest risk of serious skin reactions occurrence is especially during the first week of treatment. If you develop a severe rash or any of these skin symptoms, stop taking <medicine> and contact or see a doctor immediately.

- Section 4

Not known: frequency cannot be estimated from the available data

Generalized rash, red and scaly with bumps under the skin and vesicles associated with fever at the beginning of treatment (generalized acute exanthematous pustulosis). If you develop these symptoms stop using <medicine> and contact or see a doctor immediately.

Annex III

Timetable for the implementation of this position

Timetable for the implementation of this position

Adoption of CMDh position:	January 2020 CMDh meeting
Transmission to National Competent Authorities of the translations of the annexes to the position:	15 March 2020
Implementation of the position by the Member States (submission of the variation by the Marketing Authorisation Holder):	14 May 2020