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 permethrin, the scientific conclusions are as follows:

1. **Inclusion of a statement regarding "precautionary measures during pregnancy" for the <u>head lice indication</u>**

Based on the available data for permethrin the associated toxicity to the unborn child are not conclusive and a possible carcinogenic risk cannot be clearly excluded.

At least some of the evaluations do not exclude a carcinogenic potential of the active substance permethrin. The "Joint Meeting on Pesticide Residues" (JMPR) of the WHO/FAO evaluated permethrin in 1999 and concluded that the substance possesses very weak oncogenic potential, and remote probability of oncogenic potential in humans. The International Agency for Research on Cancer (IARC) classified permethrin as not classifiable as to its carcinogenicity to humans (Group 3), due to inadequate evidence in experimental animals. In addition the United States Environmental Protection Agency (US-EPA) assessed permethrin as "Likely to be Carcinogenic to Humans" by the oral route.

On the other hand, Yamada et al. (2017) concluded within a non-clinical study, that permethrin will not likely lead to an increase in susceptibility to lung tumour development in humans and the ICSRs assessed by Infectopharm do not show any indication of a carcinogenic potential.

Furthermore, also the systematic review by Boffetta et al. (2018) could not resolve the uncertainties regarding the carcinogenic potential of permethrin. Based on the selected studies of this systematic review, the authors concluded that permethrin exposure did not seem to entail a risk of cancer in humans. Results on multiple myeloma and childhood leukemia are weak and inconsistent, and require replication in independent populations. Therefore, also from this review especially the risk of childhood leukemia remains uncertain.

In summary, the carcinogenic risk of permethrin is neither proven nor can it be definitively excluded with the available data submitted within this PSUSA. Although one can probably assume especially from the presented calculations by Infectopharm that the cancer lifetime risk of permethrin appears to be low in children from the age of 2 months and adults when topically applied according to indication.

Nevertheless, following discussion of the risk of carcinogenicity (childhood leukaemia) in child with an in utero pesticide exposure based on the study by Ferreira et al. (2013) in the last PSUSA, new data provided within this PSUR period could not resolve the uncertainties regarding this risk.

In addition, the two studies mentioned by GSK (Kennedy 2005; Mytton 2007), which assess the exposure during pregnancy, could not exclude the risk of birth defects due to the limitation of too small sample sizes. Moreover, no conclusion can be drawn from these studies regarding the possible carcinogenic potential, since only for the small study by Kennedy 2005 (113 completed pregnancies outcomes under permethrin use) a follow-up of the cases was performed.

As it is not possible to firmly confirm or exclude a possible risk to the unborn due to the methodological limitations of previous observational studies, further studies would be highly desirable. However, the feasibility to evaluate the carcinogenic potential of permethrin-containing products via future database studies is considered to be low, because of the long latency of the outcome, the low exposure during pregnancy, the need of maternal data linkage with their children and the prescription status of the medicinal products in countries with relevant databases.

In conclusion, a possible risk to the unborn cannot be clearly excluded from all the presented data.

Besides this, with regard to the permethrin use in pregnancy there is also some evidence that shows a reduction in permethrin efficacy regarding the treatment of head lice in selected countries. In addition, there are effective physically acting treatment alternatives for head lice,.

In summary, the inconclusive data on a possible risk to the unborn child warrants that a safety-based approach is taken to avoid exposure of the unborn child especially in this indication with alternative less toxic treatment options.

2. Inclusion of a statement regarding "treatment failure and resistance development" for the head lice indication

There is a high prevalence of knockdown resistance (kdr)-like genes in head lice which are associated with increased permethrin tolerance or resistance. However, a clear correlation between this genotype and the success rate in the treatment of head lice is lacking. In many cases it is unclear whether the treatment failure is due to adaption of the lice or due to incorrect application or re-infestation. However, problems of treatment failure should be reflected in a warning statement in section 4.4. of the SmPC and considerations should be given to official guidance. Moreover, a statement regarding repeated dosing should be included in the dosing section of the SmPC and PL.

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 permethrin the CMDh is of the opinion that the benefit-risk balance of the medicinal product(s) containing permethrin 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 permethrin 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~~)**

1) **Inclusion of a statement regarding "precautionary measures during pregnancy" for the head lice indication**

The following sentence should be included in all SmPCs regarding the head lice indication:

0.43%; 0.5% and 1% permethrin (Head lice)

SmPC

4.6 Pregnancy and lactation

Pregnancy

For precautionary reasons, the use of {invented name} during pregnancy should be avoided unless physically acting treatment alternatives were ineffective and/or treatment with permethrin is required due to the woman's clinical condition.

PIL

For precautionary reasons, you should not use X during pregnancy unless your doctor advise you to do so.

2) **Inclusion of a statement regarding "treatment failure and resistance development" for the head lice indication**

0.43%, 0.5% and 1% permethrin

SmPC

4.2 Posology and method of administration

If after 7-10 days of treatment with permethrin living lice are found, treatment with permethrin should be repeated. If after 14-20 days infestation is still active treatment with an alternative product should be considered.

4.4 Special warnings and precautions for use

Treatment failure and resistance development

Varying clinical success rates to permethrin in the treatment of head lice have been observed geographically and over time. Factors associated with treatment failure include incorrect dosing or administration errors, lack of concurrent treatment of household members, and re-infestation from community contacts. Furthermore, resistance to permethrin has been detected. However, no clear correlation could be established between lack of efficacy and mutations known to confer pyrethroid resistance. Official guidance on the appropriate use of pediculicide agents should be considered.

PIL

3. How to use

If after 7-10 days of treatment with permethrin living lice are found, treatment with permethrin should be repeated. If after 14-20 days living lice are still found, the treating physician should be consulted to consider appropriate alternative treatment options.

Annex III

Timetable for the implementation of this position

Timetable for the implementation of this position

Adoption of CMDh position:	May 2019 CMDh meeting
Transmission to National Competent Authorities of the translations of the annexes to the position:	13 July 2019
Implementation of the position by the Member States (submission of the variation by the Marketing Authorisation Holder):	11 September 2019

APPENDIX I

PRAC PSUR Assessment Report