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 chlorquinaldol (vaginal tablet) / promestriene, the scientific conclusions are as follows:

The MAH was requested to present a cumulative review of the cases with vaginal bleeding, including menorrhagia and metrorrhagia, and also to include an analysis of relevant reported cases and using all sources of information (studies, literature).

Cumulatively, a safety database search identified 30 post-marketing cases of vaginal bleeding and other bleeding/haemorrhage events in patients exposed to vaginal chlorquinaldol/promestriene (search criteria: Preferred terms (PTs) “Menorrhagia”, “Metrorrhagia”, “Vaginal haemorrhage”, “Genital haemorrhage”, “Postmenopausal haemorrhage”, “Coital bleeding”). Of these 30 cases reported cumulatively, 3 cases were considered as serious and 21 cases were medically confirmed. Positive dechallenge was noticed in 11 cases (7 medically confirmed) and a positive rechallenge in 1 case, negative dechallenge was noted in 2 cases. Gynaecological examination was performed in 2 cases and concluded that the bleeding was probably due to mechanical aetiology related with the contact of the vaginal tablet with the vaginal mucous membrane considering it was atrophic, dry, irritated. The causal association of the bleeding events with the administration of promestriene/chlorquinaldol was considered by the MAH not assessable in 15 cases, unlikely in 8 cases and possible in 7 cases. Acknowledging that in most cases relevant information for proper causality assessment is missing, there are still seven cases assessed as possibly related based on plausible temporal relationship and positive dechallenge, which confirms that an association is possible or at least cannot be ruled out.

For PT vaginal haemorrhage, the MAH received 5 non-serious cases during the covered period, and 18 cases cumulatively. As vaginal bleeding is not included in the Product Information for chlorquinaldol/promestriene, and considering the cumulative data provided and the 5 new reported cases with vaginal bleeding, the suspected mechanical aetiology of bleeding and the medical condition of the treated patients that in most of the cases predispose to local injuries and bleeding, the PRAC considers that causal association between chlorquinaldol/promestriene and vaginal bleeding cannot be excluded and vaginal bleeding should be included in the product information.

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 chlorquinaldol (vaginal tablet) / promestriene the CMDh is of the opinion that the benefit-risk balance of the medicinal product(s) containing chlorquinaldol (vaginal tablet) / promestriene 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 {active substance(s) as EURD list entry} 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 revised as follows:

A full clinical and gynaecological examination should be performed before the start of treatment. Medical monitoring is necessary during treatment. ~~In the event of metrorrhagia, it is necessary to search for a cause~~**. Cases of vaginal bleeding have been reported while administering chlorquinaldol/promestriene vaginal tablets. In the event of vaginal bleeding, it is necessary to stop the treatment and search for the etiology of the bleeding.**

- Section 4.8

The following adverse reaction should be added under the SOC *Reproductive system and breast disorders* with a frequency *not known (cannot be estimated from available data)*:

Vaginal bleeding

Package Leaflet

- Section 2. What you need to know before you use

Warnings and precautions

Cases of vaginal bleeding have been reported while administering chlorquinaldol/promestriene vaginal tablets. In the event of vaginal bleeding, it is necessary to stop the treatment and consult your doctor.

- Section 4. Possible side effects

The following adverse reaction should be added with a frequency: *not known (cannot be estimated from the available data):*

Vaginal bleeding

Annex III

Timetable for the implementation of this position

Timetable for the implementation of this position

Adoption of CMDh position:	May 2017 CMDh meeting
Transmission to National Competent Authorities of the translations of the annexes to the position:	1 July 2017
Implementation of the position by the Member States (submission of the variation by the Marketing Authorisation Holder):	30 August 2017