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 promestriene (cream and vaginal capsules, the scientific conclusions are as follows:

In view of available data on hypersensitivity from spontaneous reports, including in some cases a positive de-challenge, the PRAC considers a causal relationship between promestriene (cream and vaginal capsules) and hypersensitivity is at least a reasonable possibility. The PRAC concluded that the product information of products containing promestriene (cream and vaginal capsules) should be amended accordingly.

In view of available data on vulvovaginal pruritus from spontaneous reports, including in some cases a close temporal relationship, a positive de-challenge and positive re-challenge, the PRAC considers a causal relationship between promestriene (cream and vaginal capsules) and vulvovaginal pruritus is at least a reasonable possibility. The PRAC concluded that the product information of products containing promestriene (cream and vaginal capsules) should be amended accordingly.

In view of available data on vulvovaginal burning sensation, vulvovaginal discomfort, vulvovaginal pain, vaginal discharge from spontaneous reports, including in some cases a close temporal relationship, a positive de-challenge and positive re-challenge, the PRAC considers a causal relationship between promestriene (cream and vaginal capsules) and vulvovaginal burning sensation, vulvovaginal discomfort, vulvovaginal pain, vaginal discharge is at least a reasonable possibility. The PRAC concluded that the product information of products containing promestriene (cream and vaginal capsules) 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 promestriene (cream and vaginal capsules) the CMDh is of the opinion that the benefit-risk balance of the medicinal product(s) containing promestriene (cream and vaginal capsules) 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 promestriene (cream and vaginal capsules) 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

For cream and vaginal capsules

Section 4.8.

The following adverse reaction should be amended under the SOC Immune system disorders with a frequency very rare:

~~Allergy~~ **Hypersensitivity (e.g. rash, eczema, anaphylactic reaction)**

The following adverse reactions should be added under the SOC Reproductive system and breast disorders with a frequency very rare:

Vulvovaginal pruritus

The following adverse reaction(s) under the SOC Skin and subcutaneous tissue disorders should be removed:

~~Very rare: Application site pruritus~~

The following adverse reaction(s) should be added under the SOC Reproductive system and breast disorders with a frequency unknown:

Vulvovaginal burning sensation, Vulvovaginal discomfort, Vulvovaginal pain, Vaginal discharge

Package leaflet

For cream and vaginal capsules

Section 4

The following adverse reactions should be amended:

Frequency Very rare: ~~Allergy~~ **Allergic reactions (e.g. rash, eczema, severe allergic reaction)**

Frequency Very rare: Itching **of vagina/vulva**

The following adverse reactions should be added:

Frequency unknown: **Burning sensation of vagina/vulva, discomfort of vagina/vulva, vaginal/vulvar pain, vaginal discharge**

Annex III

Timetable for the implementation of this position

Timetable for the implementation of the agreement

Adoption of CMDh agreement:	December 2021 CMDh meeting
Transmission to National Competent Authorities of the translations of the annexes to the agreement:	31 January 2022
Implementation of the agreement by the Member States (submission of the variation by the Marketing Authorisation Holder):	31 March 2022