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 estradiol (except cream/balm/emulsion for application in female genital area), the scientific conclusions are as follows:

In view of available data on risk of estradiol transfer to children and pets reported from the literature, spontaneous reports including in some cases a close temporal relationship, a positive de-challenge and/or re-challenge and in view of a plausible mechanism of action, the PRAC considers that unintentional estradiol transfer to children and pets can occur with estradiol spray/gel for transdermal use. The PRAC concluded that the product information of estradiol-containing spray/gel for transdermal use should be amended to include a warning for healthcare professionals and patients.

Detailed explanation of the grounds for the differences with the PRAC recommendation

The CMDh took into consideration that relevant provisions of Directive 2001/83 and Regulation 726/2004 do not include any references for contents of SmPC, labelling and package leaflet to concerns/warnings in the context of impact of a medicinal product on animals. As such it is not anticipated that the information on risks for animals of a medicinal product for human use is included in the product information of human medicinal products.

The CMDh agreed that information in SmPC, labelling and package leaflet should be limited to their objective of being the basis of information on how to use the medicinal product safely and effectively in humans. The CMDh has therefore revised the scientific conclusions to remove the reference to pets.

In view of available data on risk of estradiol transfer to children reported from the literature, spontaneous reports including in some cases a close temporal relationship, a positive de-challenge and/or re-challenge and in view of a plausible mechanism of action, the CMDh considers that unintentional estradiol transfer to children can occur with estradiol spray/gel for transdermal use. The CMDh concluded that the product information of estradiol-containing spray/gel for transdermal use should be amended to include a warning for healthcare professionals and patients.

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

On the basis of the scientific conclusions for estradiol (except cream/balm/emulsion for application in female genital area) the CMDh is of the opinion that the benefit-risk balance of the medicinal product(s) containing estradiol (except cream/balm/emulsion for application in female genital area) 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 estradiol (except cream/balm/emulsion for application in female genital area) 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 4.2

The wording should be amended or added for estradiol sprays and estradiol gels as follows:

Patients should be informed that children should not come in contact with the area of the body where estradiol spray/gel was sprayed/applied on (see section 4.4).

- Section 4.4

A warning should be amended or added for estradiol sprays and estradiol gels as follows:

Potential estradiol transfer to children

Estradiol spray/gel can be accidentally transferred to children from the area of the skin where it was sprayed/applied on.

Post-marketing reports of breast budding and breast masses in prepubertal females, precocious puberty, gynaecomastia and breast masses in prepubertal males following unintentional secondary exposure to estradiol spray/gel have been reported. In most cases, the condition resolved with removal of estradiol exposure.

Patients should be instructed:

- **not to allow others, especially children, to come into contact with the exposed area of the skin and to cover the application site with clothing if needed. In case of contact the child's skin should be washed with soap and water as soon as possible.**
- **to consult a physician in case of signs and symptoms (breast development or other sexual changes) in a child that may have been exposed accidentally to estradiol spray/gel.**

Package Leaflet

- Section 2

Children

Estradiol spray/gel can be accidentally transferred from the skin to other people. Do not allow others, especially children, to come into contact with the exposed area of your skin and cover the area, if needed, after the spray/gel has dried. If a child comes in contact with the area of the skin where estradiol was sprayed/applied on, wash the child's skin with soap and water as soon as possible. Due to the estradiol transfer, young children may show signs of puberty that are not expected (for example breast budding). In most cases the symptoms will disappear when children are no longer exposed to estradiol spray/gel.

Contact your healthcare provider if you see any signs and symptoms (breast development or other sexual changes) in a child that may have been exposed accidentally to estradiol spray/gel.

- Section 3

Do not allow other people to touch the area of the skin where the spray/gel was sprayed/applied until the spray/gel has dried and cover with clothing if needed.

Annex III

Timetable for the implementation of this position

Timetable for the implementation of this position

Readoption of CMDh position:	May 2022 CMDh meeting
Transmission to National Competent Authorities of the translations of the annexes to the position:	6 June 2022
Implementation of the position by the Member States (submission of the variation by the Marketing Authorisation Holder):	5 August 2022