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 dydrogesterone / estradiol, the scientific conclusions are as follows:

Scientific conclusions and grounds for variation to the terms of the marketing authorisations

In view of available data on risk of meningioma from the literature, spontaneous reports including in 2 cases a suggestive temporal relationship and stabilisation or decrease in tumor volume after drug discontinuation, and in view of a plausible mechanism of action, the PRAC considers a causal relationship between dydrogesterone/estradiol and meningioma is at least a reasonable possibility. The PRAC concluded that the product information of products containing estradiol/ dydrogesterone should be amended accordingly.

Having reviewed the PRAC recommendation, the CMDh agrees with the PRAC overall conclusions and grounds for recommendation.

Grounds for the variation to the terms of the marketing authorisation(s)

On the basis of the scientific conclusions for dydrogesterone / estradiol the CMDh is of the opinion that the benefit-risk balance of the medicinal product(s) containing dydrogesterone / estradiol is unchanged subject to the proposed changes to the product information

The CMDh recommends that the terms of the marketing authorisation(s) should be varied.

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 4.3

The contraindication/s should be added as follows:

- **Meningioma or history of meningioma.**

- Section 4.4:

Sub-section "Conditions which need supervision":

If any of the following conditions are present, have occurred previously, and/or have been aggravated during pregnancy or previous hormone treatment, the patient should be closely supervised. It should be taken into account that these conditions may recur or be aggravated during treatment with XXX, in particular:

~~- Meningioma~~

[…]

Meningioma

The occurrence of meningiomas (single and multiple) has been reported in association with use of [xxx]. Patients should be monitored for signs and symptoms of meningiomas in accordance with clinical practice. If a patient is diagnosed with meningioma, any [XXX] containing treatment must be stopped (see section 4.3). Tumour shrinkage has been observed after treatment discontinuation.

Package Leaflet

- Do not use X:
  - **if you have meningioma or have ever been diagnosed with a meningioma (a generally benign tumour of the tissue layer between the brain and the skull).**

  […]
  If any of the above conditions appear for the first time while taking XXX, stop taking it at once and consult your doctor immediately.

- Warnings and Precautions

When to take special care with XXX
Tell your doctor if you have ever had any of the following problems, before you start the treatment, as these may return or become worse during treatment with XXX. If so, you should see your doctor more often for check-ups:
[…]
~~• a tumour of the brain that may be affected by the levels of progestagens (meningioma)~~

Meningioma

Use of [xxx] has been linked to the development of a generally benign tumour of the tissue layer between the brain and the skull (meningioma). If you are diagnosed with meningioma, your doctor will stop your treatment with <Invented name> (see section 'Do not take…'). If you notice any symptoms such as changes in vision (e.g. seeing double or blurriness), hearing loss or ringing in the ears, loss of smell, headaches that worsen with time, memory loss, seizures, weakness in your arms or legs, you must tell your doctor straightaway.

Annex III

Timetable for the implementation of this position

Timetable for the implementation of this position

Adoption of CMDh position:	July 2024 CMDh meeting
Transmission to National Competent Authorities of the translations of the annexes to the position:	09 September 2024
Implementation of the position by the Member States (submission of the variation by the Marketing Authorisation Holder):	07 November 2024