Appendix to CMDh position

Divergent position to CMDh position

Article 107i of Directive 2001/83/EC

Procedure No: EMEA/H/A-107i/1357

Cyproterone acetate/ethinylestradiol (2mg/0.035mg) containing medicinal products

The following CMDh Member supports the divergent position appended to the PRAC recommendation on cyproterone acetate/ethinylestradiol (2mg/0.035mg) containing medicinal products dated 16 May 2013, as stated below:

CMDh member expressing a divergent position

Virginie Bacquet (FR)	29 May 2013	Signature: …….....

<u>Divergent statement from PRAC member</u>

The PRAC member, representative of the French National Competent Authority, co-rapporteur for the dossier, has a divergent opinion with the PRAC's recommendation on medicines containing cyproterone acetate 2 mg (CPA) / ethinylestradiol 0.035 mg (EE) (Diane and generics).

The reasons for divergent opinion are as follows:

- With respect to risk:

Since 1987, thromboembolic events were reported including fatal cases (8% of the cases reported) associated with CPA/EE mainly within the first year of treatment. Venous thromboembolism (VTE) is the most reported effect.

The PRAC member highlights that the PRAC agrees with the conclusion of an increased risk of thromboembolic events (VTE), 4 to 7 higher in female users of a combination of CPA/EE than in female non-exposed to CPA/EE or Combined Oral Contraceptives (COCs) and that this risk is assumed to be equivalent to that of non levonorgestrel COCs.

- With respect to benefit:

The assessment of the data provided during this referral shows a thin evidence of the efficacy of the product in acne and difficulties to qualify the type of acne due to the lack of standard method of acne grading used in clinical trials.

With regard to contraception, although there is a presumption of efficacy for CPA/EE as a contraceptive considering the pharmacological properties of both components, the level of efficacy demonstration is insufficient to grant an indication in contraception. The efficacy studies performed are not up to nowadays' standards.

Even if the PRAC recommendation is in favour of a positive benefit/risk ratio provided changes of the product information (SmPC and Package Leaflet), a communication plan including educational materials and two studies, a post-authorisation study and a drug utilisation study, the above Member state is of opinion that the MAHs should provide a clinical study with a robust methodology to allow the calculation of a reliable Pearl Index in order to prove its full efficacy as a contraceptive.

Diane is also indicated in hirsutism and alopecia in several EU Member States. However, there are no robust data to support these indications.

The therapeutic fields of CPA/EE containing products are heterogeneous across Europe and this unclear situation participates to the risk of incorrect handling of the drug.

- With respect to off-label use:

Data issued from French and European panel of physicians confirm the off-label use of CPA/EE containing products as a contraceptive only. Responses from patients also support this large off-label use.

The confusion remains about the labelling of indications, especially for the contraceptive effect leading to a wide off-label use exposing unnecessarily women for a longer period to an increased risk of venous thromboembolism.

Taking all these aspects into account, the benefit / risk balance of Diane 35 and other medicines containing cyproterone acetate 2 mg (CPA) / ethinylestradiol 0.035 mg (EE) is unfavourable as regards the therapeutic indications in androgen increased-sensitivity women for whom hormonal contraceptive treatment is considered appropriate.

In consequences, the above Member State expresses a divergent opinion to the proposed labelling for the therapeutic indications.