EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

11 April 2019
EMA/PRAC/214199/2019

PRAC List of questions

To be addressed by the marketing authorisation holder(s) for 0.01% w/w estradiol-containing medicinal products for topical use

Referral under Article 31 of Directive 2001/83/EC resulting from pharmacovigilance data

Procedure number: EMEA/H/A-31/1482

INN/active substance: estradiol

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1. Background

Following the recent partial annulment by the European Court of Justice on procedural grounds, not contesting the scientific findings, of the Commission Decision for the Article 31 referral on topical products containing 0.01% w/w estradiol for topical use (vaginal), a new procedure under Article 31 of Directive 2001/83/EC was triggered by the European Commission on 4 April 2019 for these products as there is a Union interest to protect public health. The high blood concentration that has been seen in PK studies for these products may pose a risk to women's health in long term use. Therefore the European Commission is of the view that the potential risk related to the use of these products would still have to be addressed through risk minimisation measures, as appropriate.

2. Questions

The marketing authorisation holders MAH(s) are requested to address the following questions:

General information

Question 1

The MAHs should provide information on marketing and legal status of their products containing estradiol 0.01%w/w for topical use in the different EU Member States (MS).

Question 2

The MAHs should submit the product information (PI) of their products containing estradiol 0.01%w/w for topical use in English. In addition the MAHs should provide a tabulated overview of the main differences, if any, between the SmPC and package leaflet in the different MSs where these products are authorised.

Question 3

The MAHs should provide figures on patient exposure of their products containing estradiol 0.01%w/w for topical use stratified by member state and presented per year during the period 2010 and 2018.

PK and efficacy

Question 4

Please provide all pharmacokinetic and efficacy data available for topical estradiol 0.01%w/w relevant to the approved doses and dosing regimen, including any comparison of these data (with respect to C_{max}, $C_{average}$ and AUC of estradiol) for their products containing estradiol 0.01%w/w for topical use compared to other topical estradiol products (e.g. Vagifem 10 mcg, Estring) and to systemic HRT estradiol products.

Safety

Question 5

The MAHs should provide a cumulative review of all reported adverse events for medicinal products containing estradiol 0.01%w/w for topical use. This review should include the provision of CIOMS forms/case narratives and causality assessment. Special attention should be paid to events that could be due to systemic exposure to these products.

Question 6

The MAHs should submit and discuss all literature data related to safety of medicinal products containing estradiol 0.01%w/w for topical use.

Question 7

The MAHs should discuss and justify based on data the appropriate duration of use for medicinal products containing estradiol 0.01%w/w for topical use in view of the fact that HRT associated risks increase with duration of treatment and oestrogen dose.

Question 8

Taking into account any systemic exposure to estradiol during treatment, the MAHs should discuss the need of adding concomitant systemic progestogen to the treatment with medicinal products containing estradiol 0.01%w/w for topical use for ensuring endometrial protection in women with a uterus.

Benefit-risk balance and risk minimisation

Question 9

Taking into account the available data on pharmacokinetics, efficacy and safety, of products containing estradiol 0.01%w/w for topical use, and also the well-known risks of systemic HRT, please discuss the impact on the benefit-risk balance of these products including any proposed risk minimisation measures in the product information and discuss how the effectiveness of these risk minimisation measures will be evaluated.