NOTIFICATION TO THE PRAC/EMA SECRETARIAT OF A REFERRAL UNDER ARTICLE 31 OF DIRECTIVE 2001/83/EC

E-mail: ReferralNotifications@ema.europa.eu

This notification is a referral under Article 31 of Directive 2001/83/EC to the PRAC made by the European Commission:

Product Name(s) in the Referring Member State, if applicable	High concentration of oestradiol containing medicinal products (and related substances) for topical use (vaginal use).
Active substance(s)	oestradiol
Pharmaceutical form(s)	Cream/emulsion for topical use (vaginal)
Strength(s)	0.01% w/w
Route(s) of Administration	Topical use (vaginal route)
Marketing Authorisation Holder(s)	Dr. August Wolff GmbH & Co. KG Arzneimittel Pharmazeutische Fabrik Montavit GesmbH

On 25 April 2014, the European Medicines Agency's Committee for Medicinal Products for Human Use (CHMP) concluded a review of the overall benefit-risk balance of high concentration oestradiol containing medicinal products indicated for topical use for the treatment of vaginal atrophy (intravaginally and on the skin of vulva and vagina) under Article 31 of Directive 2001/83/EC.

These products are used in topical applications to relieve symptoms of vaginal atrophy in postmenopausal women.

This review was initiated further to data having shown a high plasmatic level of oestradiol (comparable to oestradiol levels for products for systemic HRT) after administration for the medicinal products containing 0.01 g oestradiol per 100 g (0.01% w/w).

At that time, in view of the significant systemic exposure to oestradiol and the high dosage regimen, the CHMP had concerns about the impact of these findings on the safety profile of these products for intravaginal use and recommended a set of measures including:

- Modification of the indication to treat vaginal atrophy due to oestrogen deficiency in postmenopausal women;

- the limitation of the duration of use (4 weeks);

- to consider alternative therapies in case the symptoms re-appear, as well as an update of the contra-indications and warnings related to systemic side effects of oestradiol;

- removing from the market the larger presentation of 100g cream.

Furthermore, based on the available efficacy data, CHMP recommended the restriction of the indication to the treatment of vaginal atrophy due to oestrogen deficiency in postmenopausal women with an intravaginally application only and not on other parts of the genital area.

Further to the adoption of the Commission decision for this referral (C(2014)6030final) on 19 August 2014, an action for annulment was brought before the Court of Justice of the European Union against the Commission decision (Cases T-672/14 and C-680/16P).

On 27 March 2019, the Court of Justice partially annulled the Commission Decision holding that due to the particular circumstances of the case the handling of the review by the responsible committee of the European Medicines Agency had not ensured sufficient guarantees to exclude any legitimate doubts as to compliance with the obligation of impartiality as enshrined in Article 41 of the Charter (case C-680/16P).

The partial annulment of the Commission Decision leads to the invalidation of some of the restrictive measures that have been taken as the outcome of the above described review, even if the scientific assessment of the products was not put into question by the Court of Justice in its judgment.

The European Commission is therefore concerned that safety risks identified for those products are no longer appropriately addressed and that patients are put at a risk.

It is hence necessary to review those products again under Article 31 of Directive 2001/83/EC. Therefore, an assessment taking into account data relating to pharmacovigilance including the data considered in the context of the previous review and any further data that has emerged since 2014 including individual case reports and literature references is required.

In view of the above and the need to take an action at EU level, the European Commission considers that it is in the interest of the Union to refer the matter to the PRAC and requests that it gives its recommendation under Article 31 of Directive 2001/83/EC as to whether marketing authorisations of these products (i.e. medicinal products containing 0.01 g oestradiol per 100 g (0.01% w/w) for intravaginal use) should be maintained, varied, suspended, or revoked.

[redacted]

4/4/2019

Signed Date

Head of Unit - Medicines: policy, authorisation and monitoring
Directorate-General Health and Food Safety
European Commission