Annex II

Scientific conclusions

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On 04 April 2019 the EC triggered a procedure under Article 31 of Directive 2001/83/EC, and asked the PRAC to assess the impact of the above concerns on the benefit-risk balance of estradiol-containing (0.01% w/w) medicinal products for topical use and issue a recommendation on whether the marketing authorisation(s) of these products should be maintained, varied, suspended or revoked.

The PRAC adopted a recommendation on 16 January 2020 which was then considered by the CMDh, in accordance with Article 107k of Directive 2001/83/EC.

Overall summary of the scientific evaluation by the PRAC

The active ingredient of these products is synthetic 17β-estradiol, chemically and biologically identical to endogenous human estradiol, which is responsible for the primary and secondary female sexual characteristics. After the vaginal application, estradiol is absorbed by the vaginal epithelium where it causes the increase of numbers of surface and intermediate cells and decreases the number of basal cells. It is intended to alleviate the symptoms of vaginal atrophy or genitourinary syndrome in menopause, which is defined as a complex of symptoms and signs associated with a decrease in estrogen and other sex steroids involving changes to the labia majora/minora, clitoris, vestibule/introitus, vagina, urethra and bladder.

This review was initiated further to data having shown a high plasmatic level of estradiol (comparable to estradiol levels for products for systemic hormone replacement therapy; HRT), above the reference range values of postmenopausal serum estradiol levels described across literature (from 10 up to 50 pg/mL) after vaginal administration for the medicinal products containing 100 micrograms estradiol *per* gram.

On 04 April 2019, the EC triggered a referral under Article 31 of Directive 2001/83/EC and requested the PRAC to assess the impact of the above concerns on the benefit-risk balance of estradiol-containing (0.01% w/w) medicinal products for topical use and to issue a recommendation on whether the relevant marketing authorisations should be maintained, varied, suspended or revoked.

The scope of this procedure is limited to estradiol-containing (0.01% w/w) medicinal products for topical use (cream, emulsion).

The products are marketed in Austria, Bulgaria, Croatia, Czech Republic, Estonia, Germany, Hungary, Latvia, Lithuania and Slovakia.

On 9 December 2019 one MAH (Dr. August Wolff GmbH & Co. KG Arzneimittel) submitted detailed grounds for re-examination of the PRAC recommendation regarding the conclusions drawn on the pharmacokinetic study (study SCO 5109), the applicability of the core product information of HRT products to the product information of estradiol-containing (0.01% w/w) medicinal products for topical use and on the proportionality of the risk minimisation measures recommended by the PRAC.

Based on all the available data and having carefully assessed the grounds for re-examination, the PRAC maintained its position that the systemic exposure to estradiol above normal postmenopausal range after a single administration of estradiol-containing (0.01% w/w) medicinal products for topical use raises serious doubts on the safety risks of these products since the adverse reactions associated with a systemic exposure to estradiol cannot be excluded based on available data.

Indeed, a significant increase of systemic estradiol to five times above the upper limit of the reference postmenopausal estradiol serum levels of 10-20 pg/mL was observed as well as an increase above the upper reference limit of 50 pg/mL. In addition, elevated estradiol above the menopausal levels are observed up until 36 hours after administration.

Despite the limited data available as no dose-finding studies have been performed and only one placebo-controlled clinical study was performed to support efficacy in a limited group of patients and with limited duration of use (4 weeks), the efficacy is considered sufficiently shown in comparison to placebo over a period of 4 weeks treatment in the authorised indication.

In terms of safety, although there is a large post-marketing exposure, no definite conclusions regarding the safety profile beyond 4 weeks can be drawn based only on individual case safety reports and due to the low number of reported cases.

However, this cannot be interpreted as reassurance of lack of risk. Given the nature of these products (topical) and the fact that they have been on the market for decades, a considerable level of underreporting of ADRs may be expected. Most patients treated with estradiol 0.01% w/w are expected to be of higher age and suffer from underlying diseases, which could make it less likely to identify adverse effects as potentially related to estradiol exposure and report them.

Cases reporting of systemic ADRs after topical application of 0.01% w/w estradiol cream were identified in Eudravigilance.

In these cases, serious reactions were reported mainly on risks known to be associated with the use of estradiol in systemic HRT (breast cancer, cerebrovascular accidents and endometrial thickening). However, in most of these cases systemic HRT was used concomitantly whilst a long-term use of high concentration estradiol cream was described. Nevertheless, a potential additive effect of estradiol vaginal cream to HRT associated risks could not be ruled out.

The majority of all case reports have several confounders, and systemic ADRs related only to medicinal products containing 100 microgram estradiol per gram for intravaginal use cannot be excluded. However, due to known underreporting especially for topical products, and considering the target population (postmenopausal women with many concomitant medication and risk factors) the lack of un-confounded reports cannot be explained as a lack of risk. Furthermore, signals for the events of interest, such as carcinoma, are in general difficult to be identified, especially with a limited dataset. Although no relevant new safety concern could be identified from the current available reported data given their scarcity, definite conclusions on the safety of medicinal products containing 0.01% w/w estradiol for topical use in the post-marketing setting cannot be drawn.

Safety data from the literature is also extremely scarce. The only study (SCO 5174) which identified 83 non-serious ADRs in 29 patients out of 51 patients treated had only 4 weeks treatment. In addition, the long-term exposure to medicinal products for topical use containing 0.01%w/w estradiol is not documented. The majority of existing studies focused on low-dose estradiol products which showed different characteristics than the higher-dosed estradiol products. Overall, although the literature review did not reveal any new safety concern, there is still lack of safety information on medicinal products of 0.01% w/w estradiol for topical use when used long-term.

The PRAC consulted an ad-hoc expert group of gynaecologists and patient representatives on the clinical use of these medicinal products as well as on the duration of their use. Overall, the experts agreed that the topical use of high-strength estradiol-containing products for treatment of vaginal atrophy in postmenopausal women, if used at all, is seen as a limited second line therapeutic option, with uncertain benefits and risks compared to low-dose topical products. In addition, the experts were of the view that the use of these high-dose preparations with topical application should be limited to maximum of 4 weeks, in particular considering the systemic exposure levels reached and the very limited data available regarding the safety profile of longer-term use.

In view of the above elements, in particular the seriousness of the undesirable effects associated with systemic exposure to estradiol (e.g. risk of venous thromboembolisms, stroke, ovarian cancer endometrial carcinoma), and the fact that these medicinal products are intended to act locally and the

intended use (topical treatment of symptoms of vaginal atrophy due to estrogen deficiency), the PRAC maintained its position that the use of these products should be limited to a single treatment up to 4 weeks.

If symptoms persist beyond 4 weeks, alternative therapies should be considered.

The PRAC also evaluated the adequacy of the pack sizes of the products and concluded that the pack size of 25 g is the adequate size for the 4-week treatment cycle. Package sizes above 25 g could lead to a longer use of the product beyond 4 weeks and therefore such pack sizes should not be authorised.

The PRAC also requested that the product information is updated taking into consideration the current clinical knowledge on safety of oestrogen products for vaginal application of which the systemic exposure to the oestrogen is higher than the normal postmenopausal range especially regarding associated risks such as thromboembolism events, breast and endometrial cancers. The product information should follow the elements for oestrogen products for vaginal application of which the systemic exposure to the oestrogen is higher than the normal postmenopausal range, according to the core product information on HRT products. A distinction in section 4.8 of the SmPC between the adverse events reported for these products and the adverse event which were observed as class effect in HRT treatment was considered sufficiently clear in the Product information.

To increase awareness of HCPs and patients on the limited duration of use to 4 weeks, the PRAC requested that a boxed warning is included in the outer and inner packaging of the medicinal products. In addition, the strength of the products should be also displayed in micrograms *per* gram of cream/emulsion.

A direct healthcare professional communication was also agreed, together with a communication plan, to inform relevant healthcare professionals of the new recommendations and risk minimisation measures.

Grounds for PRAC recommendation

Whereas,

- The Pharmacovigilance Risk Assessment Committee (PRAC) considered the procedure under Article 31 of Directive 2001/83/EC for estradiol-containing (0.01% w/w) medicinal products for topical use;
- The PRAC reviewed the totality of data submitted with regard to the risk of adverse drug reactions due to systemic absorption of estradiol. This includes the responses submitted by the Marketing authorisation holders, published literature, spontaneous reporting, as well as the outcome of an ad-hoc expert group of gynaecologists and patient representatives. PRAC also considered the grounds submitted by one MAH (Dr. August Wolff GmbH & Co. KG) as basis for their request for re-examination of the PRAC recommendation;
- The PRAC considered that the efficacy of estradiol-containing (0.01% w/w) medicinal products for topical use has been sufficiently demonstrated in comparison to placebo over a period of 4 weeks treatment in the treatment of the symptoms of vaginal atrophy due to oestrogen deficiency in postmenopausal women;
- In view of the currently available data, the PRAC concluded that there is a systemic exposure above the normal post-menopausal range after topical use of estradiol-containing (0.01% w/w) medicinal products for topical use that warrants risk minimisation measures.

- The PRAC noted that safety and efficacy data on treatment longer than 4 weeks as well as repeated use of estradiol-containing (0.01% w/w) medicinal products for topical use is either lacking or extremely limited. Therefore, given limitation of the data, the systemic exposure to estradiol above normal postmenopausal range of these products and the risks associated with systemic exposure to oestrogen, these products should only be used for a single treatment period up to 4 weeks maximum;
- The PRAC also concluded that the product information should be updated to take into consideration the current clinical knowledge on safety of oestrogen products for vaginal application of which the systemic exposure to the oestrogen is higher than the normal postmenopausal range, especially regarding risks of thromboembolism events, breast and endometrial cancer;
- To minimize the risk of prolonged or repeated use and to ensure patients adherence to the recommended duration of use, the maximum package size of the medicinal product authorised should not exceed 25 g;
- Finally, the PRAC concluded that the product information should be updated to increase awareness on the strength of these medicinal products and on the maximum treatment period. In addition, a direct healthcare professional communication to highlight the restricted use and warnings was agreed, together with the timelines for its distribution.

In view of the above, the PRAC concluded, in view of the available data including the detailed grounds submitted by Dr. August Wolff GmbH & Co. KG during the re-examination phase, that the benefit-risk balance of estradiol-containing (0.01% w/w) medicinal products for topical use remains favourable subject to changes to the product information and other risk minimisation measures as described in this recommendation.

CMDh position

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

Overall conclusion

The CMDh, as a consequence, considers that the benefit-risk balance of estradiol-containing (0.01% w/w) medicinal products for topical use remains favourable subject to the amendments to the product information described above.

Therefore, the CMDh recommends the variation to the terms of the marketing authorisations for estradiol-containing (0.01% w/w) medicinal products for topical use.