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Pharmacovigilance Risk Assessment Committee (PRAC)

Assessment report

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

Estradiol-containing (0.01% w/w) medicinal products for topical use

Procedure no: EMEA/H/A-31/1482

Note:

Assessment report as adopted by the PRAC and considered by the CMDh with all information of a commercially confidential nature deleted.

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1. Information on the procedure

On 25 April 2014, the EMA's Committee for Medicinal Products for Human Use (CHMP) concluded a review of the overall benefit-risk balance of estradiol (0.01%) containing medicinal products indicated for topical use for the treatment of vaginal atrophy (intravaginally and on the skin of vulva and vagina) at the request of Germany (BfArM) in June 2012.

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

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

- Modification of the indication to restrict to 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 estradiol;

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

Meanwhile in 2017 the core product information for HRT products[1] was discussed and updated in line with the available scientific knowledge taking into account the outcome of the CHMP referral.

Further to the adoption of the Commission Decision for this referral, an action for annulment was brought before the Court of Justice of the European Union against the Commission decision. The Court of Justice partially annulled the Commission Decision based on procedural grounds related to the nomination of the CHMP Rapporteurs.

Following this annulment, the European Commission considered necessary to address the potential risk related to the use of these products and to define risk minimisation measures as appropriate. Therefore, an assessment taking into account all the available data, including any data that has emerged since 2014, is required.

On 04 April 2019 the EC therefore triggered a referral under Article 31 of Directive 2001/83/EC and requested the PRAC to assess the impact of the systemic exposure on the benefit-risk balance of medicinal products containing estradiol 0.01%w/w 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 includes estradiol-containing (0.01% w/w) medicinal products (also referred as medicinal products containing 100mcg estradiol per 1g) for topical use pharmaceutical forms of cream and emulsion.

[1] Hormone replacement SmPC and Package leaflet - https://www.hma.eu/104.html

2. Scientific discussion

2.1. Introduction

Active ingredient of the products under the scope of the referral is synthetic 17β-estradiol, chemically and biologically identical to endogenous human estradiol, which is responsible for the primary and secondary female sexual characteristics.

The current indication of these products is "Treatment of vaginal atrophy due to estrogen deficiency in postmenopausal women."

After 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.

Associated decrease in estrogen and other sex steroids might lead to a complex of symptoms and signs involving changes to the labia majora/minora, clitoris, vestibule/introitus, vagina, urethra and bladder. Symptoms of the syndrome may include dryness, burning, and irritation; sexual symptoms of lack of lubrication, discomfort or pain, and impaired function; and urinary symptoms of urgency, dysuria and recurrent urinary tract infections.

The medicinal products subject to this procedure (0.01%w/w for topical use) are intended to alleviate the symptoms of vaginal atrophy due to menopause. They are currently registered in two different pharmaceutical forms: vaginal cream and vaginal emulsion.

Pharmazeutische Fabrik Montavit Ges.M.B.H is the MAH for Linoladiol Estradiol-Emulsion authorised and marketed in Austria. Pharmazeutische Fabrik Montavit Ges.M.B.H is also the MAH for Montadiol 0.01% (cream for vaginal use), authorised but not marketed in Austria, and it is designated for export in non-EU countries.

Dr. August Wolff GmbH & Co. KG Arzneimittel is the MAH of two medicinal products.

Linoladiol N (vaginal cream) is marketed in seven EU member states (Bulgaria, Croatia, Czech Republic, Estonia, Germany, Latvia and Lithuania) and also authorised but not marketed in two other European countries (Hungary, Slovakia).

Estradiol Wolff 0.01% Crème is authorised but not marketed in Germany.

Due to the different treatment duration before 2014, it is difficult to estimate patient exposure based on the number of sold packages. After the implementation of 2014 referral recommendation regarding the treatment duration limited to 4 weeks and withdrawal of packages of larger size (> 25 g), over 600,000 patients were exposed to estradiol 0.01%w/w for topical use for the period 2016-2018.

Presented data on the number of sold products indicate, that in general number of 25 g packages sold after 2015 is lower or comparable to the number of packages of larger size sold in pre-referral period.

2.2. Clinical aspects

2.2.1. Pharmacokinetics

Reference values for estradiol in postmenopausal women

The reference range values of postmenopausal serum estradiol levels vary across literature from 10-20 pg/mL (Clinical Gynaecologic Endocrinology and Infertility, 8ed, Marc A Fritz and Leon Speroff, Chapter

17 page 690: menopause and the perimenopausal transition, p690), to 10-40 pg/mL (Notelovitz et al. 2002)[2] and up to 50 pg/mL (Vagifem Clinical Pharmacology and Biopharmaceutics Review 1998).

In this assessment report, data are held, in first instance, against the reference range of 10-20 pg/mL, since it is known that in clinical practice, an estradiol reference value range in postmenopausal women of <10-60 pmol/L is used, which is similar to ~3-16 pg/mL estradiol (https://www.nvkc.nl/algemeen-overzicht-referentiewaarden - website in Dutch, Netherlands Society for Clinical Chemistry and Laboratory Medicine).

It is furthermore noted that the inclusion criteria applied in the two studies submitted by one MAH include a plasma estradiol level of <10 pg/mL as confirmation of the postmenopausal state.

Pharmacokinetics data

Two MAH-sponsored PK study reports on Linoladiol N, public literature with PK data of estradiol of Vagifem 25 mcg vaginal tablets and a tabulated overview of other estradiol containing products for vaginal, oral and dermal use were provided in the responses by the MAH Dr. August Wolff GmbH & Co. KG Arzneimittel.

Study SCO 5109 – a single dose study

Study SCO 5109 was a single dose full pharmacokinetic study to determine the systemic exposure of estradiol from Linoladiol N cream in 16 healthy postmenopausal women aged 45-70 with plasma estradiol levels of <10 pg/mL. A single dose of 2.0 g of the Linoladiol N cream was vaginally administered. Blood samples were taken from 0-36 hours after administration of Linoladiol N.

The results for estradiol were as follows:

- mean (SD) AUC_{0-36}: 1285.2 (362.1) pg/mL·h
- mean (SD) C_{max}: 103.5 (37.7) pg/mL
- mean t_{max}: 6.81 hours
- mean (SD) concentration at 24 h: 14.5 (7.2) pg/mL
- mean (SD) concentration at 36 h (C_{min}): 10.7 (3.9) pg/mL
- Average serum concentration: 33 pg/mL (calculated for a dosage interval of 24 hours, predicted under the assumption of linear PK).

Although there is only data of a single dose full PK study available, when looking at the C_{max} of 103.5 pg/mL estradiol, a significant increase to five times above the upper limit of the reference postmenopausal estradiol serum levels of 10-20 pg/mL but also above the upper reference limit of 50 pg/mL has been observed after vaginal application of a single-dose Linoladiol N cream. Also the calculated average serum concentration for a dosage interval of 24 hours ($C_{average}$) of 33 pg/mL lies substantially above the reference range of 10-20 pg/mL, which is of concern. Systemic effects due to vaginal absorption of estradiol after use of Linoladiol N cream can therefore be expected.

Study SCO 5174 – a multiple dose study

In this randomised, double-blind, placebo-controlled parallel group study efficacy and safety of Linoladiol N in 48 postmenopausal women with vaginal atrophy was evaluated. Estradiol concentration was a secondary endpoint. On days 1, 3, 5, 8, 12, 15, 19, 22, 26, and 29, 2.0 g of Linoladiol N

[2] Notelovitz M et al. Estradiol absorption from vaginal tablets in postmenopausal women. Obstetrics & Gynecology 2002; 99 (4): 556-562

(corresponding with 200 mcg estradiol) was self-administered intravaginally. The estradiol serum levels were determined on day 1 (before first dosing), day 17 and day 31.

The baseline estradiol concentrations were very low with a mean (SD) of 6.4 (8.6) pg/mL. Under treatment, the mean (SD) concentrations increased to 13.2 (13.5) pg/mL and 15.1 (13.6) pg/mL on day 17 and day 31, respectively. These estradiol values measured at days 17 and day 31 are within the postmenopausal range of 10-20 pg/mL. However, these values are through levels only (i.e. samples taken at least 36 hours after the last application). Instead, C_{max} estradiol levels would be the values of interest here and should have been shown to be within the postmenopausal range as well. This parameter is, however, not measured in this study, which makes it difficult to draw conclusions on the magnitude of systemic exposure based on the current PK study data, although a C_{max} above the reference values is likely. Of note, there was a trend noted towards lower follicle-stimulating hormone (FSH) and luteinizing *hormone* (LH) levels, which could be the consequence of systemic exposure.

Comparison with other PK data available in public literature and in the corresponding SmPCs

The study of Dickerson and colleagues (1979)[3] was a double-blind parallel study investigating intravaginal administration of conjugated estrogen cream versus estradiol cream for 14 days in 29 postmenopausal women providing clinical trial data on the recommended intravaginal dose of 200 mcg estradiol. During this period, mean (SD) estradiol levels increased from 19.25 (8.79) to 70.4 (7.85) pg/mL at day 15. The findings in this study support the conclusions obtained from studies SCO 5109 and SCO 5174. When intravaginal estradiol cream is dosed as 200 mcg estradiol, systemic exposure can be expected with estradiol levels exceeding the upper limit of the normal postmenopausal estradiol reference values 10-20 pg/mL, also above the upper reference limit of 50 pg/mL. However, due to lack of information on dosing schedule and sampling time, the data in this study are insufficient to draw definite conclusions.

The MAH Dr. August Wolff GmbH & Co. KG Arzneimittel provided a tabular overview on pharmacokinetic data (extracted from the product information) of all available estradiol-containing medicinal products. They have been categorized by route of administration, i.e. dermally, orally and vaginally applied products.

Comparability of pharmacokinetic data of different medicinal products should be done with caution. Indeed, possible differences in routes of administration, dosage forms, dose, assessment methods, presentation of pharmacokinetic results and whether these were obtained in multiple or single-dose studies limit the possibility of comparison between these studies. Orally and dermally applied products are used for systemic treatment and are therefore dosed to achieve an increase in plasma estradiol level.

Nevertheless, when looking at the dosing of the vaginally applied estradiol containing products only, a large difference is observed. The recommended maintenance dose for Linoladiol N as mentioned in its SmPC is 2 g cream = 200 mcg estradiol twice weekly = 400 mcg estradiol/week. This dose regimen is roughly 20 times higher than the dose of Vagifem 10 mcg vaginal tablets (which is 10 mcg estradiol twice weekly = 20 mcg estradiol/week) and as also stated by the MAH, 8 times higher than the dose of Vagifem 25 mcg vaginal tablets (of 1 vaginal tablet of 25 mcg estradiol twice weekly = 50 mcg estradiol/week), and the dose of Estring (which is 1 vaginal insert every 3 months with a release rate 7.5 mcg estradiol /24 hours = 52.5 mcg estradiol/week).

[3] Dickerson J, Bressler R, Christian CD, Hermann HW. 1979. Efficacy of estradiol vaginal cream in postmenopausal women. Clin Pharmacol Ther, 26:502-7

Moreover, reviewing the original study report of study SCO 5109, the investigators conclude that:

> *"In the table presenting an overview of literature, C_{max} and $C_{average}$ values of estradiol have been summarised for different routes of application and formulations. It becomes evident that the extent of estradiol exposure within a 24 hours interval after a single dose of Linoladiol N lies slightly below that obtained with different transdermal patches. But it exceeds considerably the amount obtained with a low dose of an intravaginal tablet. The table demonstrates that all percutaneous formulations including those claimed to act topically result in a systemic exposure of estradiol."*

Furthermore, the MAH provided a table in which estradiol PK parameters of the Linoladiol N are compared with published PK data obtained with Vagifem 25 mcg, as presented here above.

Table.1 Tabular overview

Medicinal product	**Dose of estradiol (E2)**	**Administration**	**Mean AUC (pg/mL*h)**	**Mean C_{max} (pg/mL)**	**$C_{average}$ (pg/mL)**	**References of PK parameters**
Linoladiol N (vaginal cream)	200 mcg	Intravaginal	1285.2[1]	103.5[3]	33[5]	Single dose study SCO 5109
Vagifem (Vaginal tablet)	25 mcg	Intravaginal	563[2]	49[4]	23[6]	Steady state study Notelovitz et al, 2002

[1] AUC_{0-36h} after single dose

[2] AUC_{0-24h} after 12 weeks of treatment (steady state)

[3] after single dose

[4] after 12 weeks of treatment (steady state)

[5] after single dose, for a dosage interval of 24 hours predicted under the assumption of linear PK

[6] after 12 weeks of treatment (steady state), concentration over 24 hours

The data in the table allow a more reliable comparison, despite that this concerns a comparison of single-dose vs multiple-dose data (as for Linoladiol N this is the only data available) and that the AUC of Linoladiol N was taken over 36 hours, while for Vagifem 25 mcg was taken over 24 hours. While acknowledging these differences, the AUC and C_{max} of estradiol with use of Linoladiol N remain substantially higher compared to Vagifem 25 mcg, which is expected as the dose recommendations for Linoladiol N are eight times higher compared to that of Vagifem 25 mcg. Most importantly, the C_{max} and $C_{average}$ values of Linoladiol N are higher than the postmenopausal reference range of 10-20 pg/mL estradiol.

Conclusions on pharmacokinetics

Although PK data of topical estradiol in concentration of 100 mcg/g are limited, the PK parameters of Linoladiol N are substantially higher compared to other vaginally applied estradiol products. The C_{max} and $C_{average}$ values of 100 mcg/g topical estradiol are also substantially higher than the postmenopausal reference range of 10-20 pg/mL estradiol (and also C_{max} above the upper reference limit of 50 pg/mL). This points towards a substantial systemic exposure of estradiol after vaginal application.

Therefore, topical estradiol in concentration of 100 mcg/g should be categorized as an estradiol product for vaginal application of which the systemic exposure to the estrogen is higher than the normal postmenopausal range.

Subsequently, the Core SmPC for HRT *elements for estrogen products for vaginal application of which the systemic exposure to the estrogen is higher than the normal postmenopausal range* applies to Linoladiol N and medicinal products containing similar strengths. *A contrario*, the Annex I of this reference document is not applicable for this product.

2.2.2. Efficacy

Medicinal products containing 0.01%w/w estradiol are considered effective in the treatment of vaginal atrophy due to oestrogen deficiency.

Nevertheless, the indication should be amended according to the Core SmPC (March 2017) as "Treatment of symptoms of vaginal atrophy due to oestrogen deficiency in postmenopausal women" which reflects that the treatment relates to the alleviation of symptoms.

As the experience treating women older than 65 years is limited, this information should also be included in the section 4.1 of the SmPC.

The relevant data on efficacy are described below.

Clinical studies

One placebo-controlled study (SCO 5174 (2004)) has been performed with Linoladiol N in the recommended dose regimen with a duration of 4 weeks. The study included 24 patients in the Linoladiol N and 24 patients in the placebo group.

The results of pharmacodynamic parameters (increase in Vaginal Maturation Index, decrease in pH) and the improvement of symptoms due to vaginal atrophy, show adequate efficacy of Linoladiol N in the approved indication.

Whilst the data is limited, the efficacy is considered sufficiently shown in comparison to placebo over a period of 4 weeks treatment, taking also into consideration the well-established use of vaginally applied estradiol.

It is noted that in the absence of any comparison to lower dosed vaginally applied estradiol products that were available on the market in 2004 (when the study was performed), it is unclear whether this high dose has superior efficacy over lower dosed vaginal estradiol products.

This dose regimen (200 mcg estradiol every other day and twice weekly thereafter) is approximately 20 times higher than the dose of Vagifem 10 mcg vaginal tablets (which is 10 mcg estradiol twice weekly = 20 mcg estradiol/week), 8 times higher than the dose of Vagifem 25 mcg vaginal tablets (1 vaginal tablet of 25 mcg estradiol twice weekly = 50 mcg estradiol/week), and the dose of Estring (1 vaginal insert every 3 months with a release rate 7.5 mcg estradiol/24 hours = 52.5 mcg estradiol/week). Although to some point efficacy is expected to increase with increasing dose, it cannot be assessed whether with a dose as high as 200 mcg, additional efficacy can be obtained.

It is noted that no data on efficacy for more than 4 weeks is available; although it is expected that these products may be efficacious for longer period, there is no data to support efficacy beyond 4 weeks.

Dose finding

No dose-finding studies have been performed by the MAHs. A rationale for the selection of the dose of 200 mcg estradiol (i.e. 2 grams of cream) to be applied every other day in the first week of treatment, i.e. at 48-hourly intervals, and twice weekly thereafter (maintenance dose) was not provided.

A specific patient group who would need such high estradiol dose while other far lower doses are available, has not been defined.

Conclusion on efficacy

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) but in view of the well-established use of vaginally applied estradiol, it is considered that the efficacy of vaginally applied 100 mcg/g estradiol containing medicinal products is sufficiently demonstrated in the authorised indication for up to 4 weeks of treatment.

No appropriate dose-finding studies have been performed.

The indication though should be amended according to the Core SmPC as "Treatment of symptoms of vaginal atrophy due to oestrogen deficiency in postmenopausal women" which reflects that the treatment relates to the alleviation of symptoms. As the experience treating women older than 65 years is limited, this information should also be included in the section 4.1 of the SmPC.

2.2.3. Safety

A. Safety data from study SCO 5174

Of the 51 patients treated, approximately half of the patients reported an adverse event in both groups. Twenty five of the 34 events during Linoladiol N treatment were classified as possibly related to the treatment. The most frequently reported adverse events belonged to the group "reproductive system", especially vaginal (e.g. itching, burning, discharge) and pelvic location (e.g. tension in the underbelly). There were no serious adverse events reported. This adverse event pattern for Linoladiol N seems comparable with that known for other vaginally applied estradiol medicinal products.

No significant change in mean endometrium thickness between screening (2.7 and 3.0 mm for Linoladiol N and placebo) and final (3.4 and 3.2 mm for Linoladiol N and placebo) examination was observed. It is noted that min-max values have not been provided.

Based on these very limited clinical data, (a small patient group and only 4 weeks treatment duration) no conclusions can be definitely, drawn on endometrial safety during prolonged use of Linoladiol N.

B. Post marketing safety data

Line listings were submitted by MAH (Dr. August Wolff GmbH & Co. KG Arzneimittel) displaying a cumulative review of all adverse drug reaction reports/cases, a PSUR (incl. PRAC assessment) and a signal detection report. Data provided by both MAHs were assessed together with the results of complementary EVDAS search performed by EMA.

i. Data submitted by the MAHs

The MAH Pharmazeutische Fabrik Montavit provided a table with 7 case reports, all reported by patients; five of them are off-label use with no ADRs.

From the 2 remaining cases associated with ADRs, one report relates to a 73-year old woman experiencing dizziness, nausea, headache, chest pain after third application of Linoladiol Estradiol-emulsion. In the second case a 21-year old woman experienced mood swings, inner restlessness and headache on the day of Linoladiol Estradiol-emulsion treatment initiation.

The MAH Dr. August Wolff GmbH & Co. KG Arzneimittel provided a table with 40 case reports. Only 36 of provided cases were related to Linoladiol N. Two of these 36 cases were considered serious adverse drug reactions. For both cases, the MAH considered that causal relationship was not assessable due to lack of information.

Overall it is agreed that data is limited and no concrete conclusion can be drawn from this.

PSUR data

As part of the MAH Dr. August Wolff GmbH & Co. KG Arzneimittel response, the PSUR covering the period from 17 January 2011 to 24 April 2017 was submitted. Data presented in the PSUR do not add any additional information to the cases assessed above.

Signal detection report

This report covers the data for period from 24 April 2018 to 24 April 2019 (=interval), taking into account the cumulative data starting in 2003 as well. The data taken into consideration included spontaneous reports (direct reports), reports from regulatory authorities as well as case reports and studies identified in the worldwide literature related to vaginal use of estradiol. Additionally, EudraVigilance was screened for relevant case reports for vaginally used estradiol.

During the signal detection period under review, a total of 10 adverse events (all non-serious) have been reported from post-marketing data sources. These included pruritus (1), amenorrhoea (1), dizziness (1), disturbance in attention (1), joint swelling (1), arthralgia (2), lymphadenopathy (1), abdominal pain (1), flatulence (1). No literature reports have been identified during the interval that concerns use of Linalodiol N.

In the signal detection report no relevant information was identified.

ii. Eudravigilance data

A global search in EudraVigilance database to identify relevant ICSRs and performed their qualitative review, was performed (cut-off date: 31 May 2019).

The following search criteria were used:

Active substance (High Level) Estradiol

EudraVigilance post-authorisation module (EVPM) cases.

Administration Route Topical and vaginal or Pharmaceutical form Vaginal creme

This EudraVigilance query returned a total of 925 case reports, 912 for topical or vaginal route of administration and 13 for pharmaceutical form vaginal creme.

ICSRs with only topical estradiol containing product for skin application listed as suspected drug were excluded.

Remaining 231 case reports where then manually reviewed according to the following methodology:

Exclusion of further cases with route of administration on skin if it is not with estradiol 0.01% w/w based on the information provided in the narrative.

As a result of this qualitative review 56 ICSRs were identified, in 18 of them it is not clear if these are related to estradiol 0.01% w/w creme or to other vaginal/topical medicinal products. 37 ICSRs are clearly related to 0.01% w/w estradiol for vaginal use. 12 out of 37 ICSRs are identical to those provided by the MAHs.

From the 37 ICSRs relevant for 0.01% estradiol for vaginal use, 27 ICSRs are serious.

Risks known to be associated with the use of estradiol in systemic HRT - i.e. endometrial hyperplasia/carcinoma, breast and ovarian cancer and thromboembolic events

From these 37 cases, 7 cases identified containing ADRs related to breast cancer and 1 case described as intraductal proliferative breast lesion; in all these cases concomitant use of co-suspect oral HRT was reported, and 2 cases reported also long-term use of medicinal products containing 100 mcg estradiol per 1g for intravaginal use- duration of 1 and 5 years.

Three (3) cases with ADRs potentially indicative of thromboembolic events were identified (2 cerebrovascular accidents and transient ischemic attack), in 2 of them concomitant HRT was reported, in one of these cases long-term use of estradiol100 mcg/g for vaginal use lasting over 2 years was reported.

Three (3) cases containing ADRs related to endometrial safety (2 cases reporting endometrial thickening and 1 case of postmenopausal bleeding for which the results of ultrasonography (USG) and hysteroscopy were pending at the time of the reporting) were found, all of them reported co-suspect oral HRT, all 3 cases reported prolonged use of the treatment ranging from 6 months to "many years"(as per case narrative).

Fourteen (14) cases reporting risks known to be associated with the systemic estradiol HRT (endometrial hyperplasia/carcinoma, breast cancer, thromboembolism) were identified. In all but one case, other concomitant HRT was reported, however additive effect of estradiol in concentration of 100 mcg/g for intravaginal use cannot be ruled out.

As the clinical experience is limited to 4 weeks and long-term safety was not investigated, six of these cases reporting prolonged use are of particular interest.

While acknowledging the low number of reported cases, limitation of spontaneous reporting (especially in identification of oncological ADRs) must be taken into account. Many patients treated with estradiol 100 mcg/g for intravaginal use could have underlying diseases and older age which makes it less likely that adverse effects would be identified as potentially related to estradiol exposure and as such reported. In addition, especially with older and topical medicinal products, substantial under-reporting of adverse effects has to be assumed.

Long-term use

Eight (8) cases of long-term use for which the length of the exposure was provided, were identified among 37 reviewed EVDAS cases. As discussed above, 6 of them were associated with estradiol related risks. Concomitant HRT was reported in 6 cases. Seven (7) cases were assessed as serious.

Where described, duration of therapy ranged from 6 weeks to 5 years. Information about the additive treatment with progesterone was provided for 1 case only - no progesterone was used.

Four (4) of these cases were reported after the finalisation of CHMP referral on topical estradiol in 2014 which concluded on the limitation of the treatment duration to 4 weeks; 2 of these cases are from EU Member States and 2 are cases from USA.

Other ADRs potentially pointing to the systemic exposure to estradiol

The review of the 37 identified cases revealed 16 cases reporting ADRs listed for estradiol products for systemic use (other than 14 main estrogen-associated risks cases discussed separately in the section above). These 16 cases potentially indicate systemic reactions to estrogens such as breast pain, headache, alopecia, muscle spasm, dizziness, nausea, mood swings, abdominal pain and arthralgia.

In 11 out of 16 cases no concomitant HRT product was reported, 5 of which were assessed as serious.

This overview might be considered as a supplementary evidence of possible systemic ADRs resulting from systemic levels of estradiol after topical application of high dose estradiol creams.

Overall conclusion on post marketing data

Although there is a large post-marketing exposure, no definite conclusions regarding safety can be drawn based only on individual case safety reports, due to the low number of reported cases.

Fourteen (14) cases reporting risks known to be associated with the use of estradiol in systemic HRT (endometrial hyperplasia/carcinoma, breast cancer, thromboembolism) were identified. In all but one case, other concomitant HRT was reported, however additive effect of high estradiol in concentration of 100 mcg/g for intravaginal use cannot be completely ruled out.

Bearing in mind that long-term safety of high concentration estradiol topical products for vaginal application was not systemically studied for period longer than 4 weeks, 8 cases reporting prolonged use are of particular interest. Reported treatment duration in these cases ranged from 6 weeks to 5 years. Seven (7) cases were assessed as serious, 6 of them reported estradiol associated risks. Concomitant HRT treatment was reported in all 6 cases, however potential additive effect of topical high concentration estradiol cannot be completely ruled out.

At least 2 cases of prolonged use were reported from EU Member States after the finalisation of CHMP referral procedure under Article 31 of Directive 2001/83/EC in 2014 which restricted the maximum treatment duration to 4 weeks. As vaginal atrophy is a chronic condition, there is reasonable assumption that high concentration estradiol products might be used in prolonged or repeated cycles instead of switching to alternative treatments as per the product information.

Under-reporting of adverse reactions are more common for topical and older products and should be considered. Many patients treated with estradiol 0.01% w/w could 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. Furthermore, signals for the events of interest, such as carcinoma, are in general difficult to be identified, especially with a limited data-set. Although no relevant new safety concern could have been identified from the current available data, given the scarcity of data, definite conclusions on the safety of estradiol in concentration of 100 mcg/g in the post-marketing setting cannot be drawn.

C. Published literature

A search in published literature was done for all relevant safety information on medicinal products containing 0.01% w/w estradiol for topical use and the main points identified are discussed below.

Systemic exposure of vaginally applied estrogens

According to North American Menopause Society (NAMS) the first step in the treatment of vaginal atrophy should be non-hormonal vaginal lubricants and moisturisers, and continued sexual activity which helps maintain active blood flow as well as production of vaginal lubrication ("Management of symptomatic vulvovaginal atrophy," 2013). However, for women with moderate to severe symptoms of

vaginal atrophy the non-hormonal therapy could be insufficient. Low dosed vaginally applied estrogens provide an alternative of a systematic hormonal therapy with relatively lower number of adverse effects.

The vaginal estrogen products are associated with better improvement of symptoms of vaginal atrophy in comparison to systemic estrogen treatment. Moreover, vaginal administration of estrogens avoids the liver first pass effect, allowing lower dosage to be used with the same effect (Kalentzi and Panay, 2005)[4] and potentially decreasing risks associated with systemic use of estradiol/progestogen. Moreover, intravaginally administered estrogens are absorbed by vaginal epithelium causing increasing epithelial proliferation with desquamation of superficial eosinofilic cells which helps maintaining ideal living conditions for lactobacilli and lower vaginal pH (Mazur et al., 2005)[5]. Additionally, unike systemic use of estrogens, vaginally applied low-dosed estrogens do not have to be combined with a progestogen to protect the endometrium from hyperplasia and cancer. With regards to pharmacokinetic data, the estradiol creams containing 100 mcg estradiol per g correspond rather to medium-dose estradiol products for systemic use.

This should be taken into consideration while extrapolating these findings to estradiol in concentration of 100 mcg/g for intravaginal application.

There are several studies which focused on systemic absorption of vaginally administered estradiol but in most of them low-dose estradiol medicinal products were used.

The low-dose vaginal estrogen theraphy is generally well tolerated and it is also effective in relieving symptoms of vaginal atrophy.

Deutsch and colleagues (1981) compared systemic absorption of vaginally and orally administered conjugated estrogens and observed different absorption patterns. Forty-six (46) patients were divided into groups treated by conjugated estrogen preparations, i.e. Premarin 0.3 mg conjugated estrogen, 0.625 mg or 1.25 mg, either orally or vaginally. For each dose studied, lower increase in blood estrogen after vaginal application compared to orally administered preparations was observed. After 1 week of therapy with 0.3 mg of vaginally administered cream no systemic absorption was detected. Decreasing the dosage of estrogens and administration of vaginal compared to oral formulations substantially lowered blood levels. (Deutsch et al, 1981)[6].

Dorr and colleagues (2010) discussed that mean unconjugated plasma estradiol and estrone cmax at steady-state were 2-3-fold higher than mean baseline endogenous estrogen after vaginal application and 3.5 – 5-fold higher than mean oral application. However, Dorr and colleagues (2010) concluded that steady-state plasma concentration of E2 and estron are lower after vaginal application compared with oral administration. Steady-state estrogen concentration after daily administration is within or slightly above the normal postmenopausal reference range which is 20 pg/ml.

An interesting finding was that the relative vaginal bioavailability of unconjugated (free) estrogen was higher (~70%) than for total (conjugated plus free) estrogens (~35%). However, the unconjugated form of estrogen is biologically active. Less than 10% of plasma estrogens are in the unconjugated form, regardless of the route administered. The observed higher vaginal bioavailability for

[4] Kalentzi, T., Panay, N., 2005. Safety of vaginal oestrogen in postmenopausal women. Obstet. Gynaecol. 7, 241–244. https://doi.org/10.1576/toag.7.4.241.27118

[5] Mazur, D., Vens-Cappell, B., Lohmann, K., Breckwoldt, M., 2005. Fraktionierte Anwendung einer 17β Estradiolcreme zur Behandlung der atrophischen Kolpitis postmenopausaler Frauen. Geburtshilfe Frauenheilkd. 65, 584–589. https://doi.org/10.1055/s-2005-865703

[6] Deutsch, S., Ossowski, R., Benjamin, I., 1981. Comparison between degree of systemic absorption of vaginally and orally administered estrogens at different dose levels in postmenopausal women. Am. J. Obstet. Gynecol. 139, 967–968. https://doi.org/10.1016/0002-9378(81)90972-8

unconjugated estrogen may be due to the fact that the first pass effect that occurs after oral estrogen administration is avoided when estrogens are absorbed via the vagina (Dorr et al., 2010)[7].

As conclusion, presented studies and literature suggest that vaginally administered medicinal products containing estradiol are absorbed systematically and very rapidly in dependency on the dose of applied estradiol. The advantage of this estradiol preparation is local effect directly in vagina as well as direct vaginal absorption on the relatively large area bypassing the liver first pass effect.

The published studies investigating pharmacokinetic properties of estradiol products both for vaginally applied or systemic administration differ considerably in study design (single or multiple administration, treatment duration, sampling, analytical method, pharmacokinetic variables). From these data, only loose estimates of the pharmacokinetic profile of different products can be made.

Safety in the published literature

The majority of the published studies are focused rather on the efficacy than on safety, and on the low dose products. However, several publications revealed some adverse effects. Dickerson and colleagues (1979)[3] concluded that incidence of side effect was low and involved breast tenderness, hot flashes, headache and abdominal cramping, menses and backache. Five out of 71 enrolled patients discontinued treatment due to symptoms related to the cream such as vaginal inflammation (Gordon, 1979)[8].

Mazur (study SCO 5174) discussed adverse effect observed during treatment by vaginal estradiol cream in concentration of 100mcg/g for 4 weeks. Overall, 29 out of 51 patients showed 83 unwanted effects but none being severe.

Twenty five of the 34 events during Linoladiol N treatment were classified as possibly related to the treatment. The most frequently reported complaints belonged to the group "reproductive system", especially vaginal (e.g. itching, burning, discharge) and pelvic complaints (e.g. tension in the underbelly). There were no serious adverse events reported. This adverse event pattern for Linoladiol N seems comparable with that known for vaginally applied estradiol products.

No significant change in mean endometrium thickness between screening (2.7 and 3.0 mm for Linoladiol N and placebo) and final (3.4 and 3.2 mm for Linoladiol N and placebo) examination was observed. It is noted that min-max values have not been provided. (Mazur, 2005)[2].

Bachmann (2008) analysed endometrial thickness by endometrial biopsies and in all cases was endometrial thickness 5 mm or less (Bachmann, 2008)[9]. In the same way, Weisberg and colleagues (2005) observed no changes in the mean endometrial thickness during 12 months treatment of ESTring (2 mg micronized estradiol in silastic ring) and Vagifem (25 mcg estradiol) (Weisberg et al, 2005)[10].

[7] Dorr, M.B., Nelson, A.L., Mayer, P.R., Ranganath, R.P., Norris, P.M., Helzner, E.C., Preston, R.A., 2010. Plasma estrogen concentrations after oral and vaginal estrogen administration in women with atrophic vaginitis. Fertil. Steril. 94, 2365–2368. https://doi.org/10.1016/j.fertnstert.2010.03.076

[8] Gordon, W.E., Hermann, H.W., Hunter, D.C., 1979. Safety and efficacy of micronized estradiol vaginal cream. South. Med. J. 72, 1252–1253, 1258.

[9] Bachmann, G., Lobo, R., Gut, R., Nachtigall, L., Notelovitz, M., 2008. Efficacy of Low-Dose Estradiol Vaginal Tablets in the Treatment of Atrophic Vaginitis: A Randomized Controlled Trial. Obstet. Gynecol. 111, 67–76. https://doi.org/10.1097/01.AOG.0000296714.12226.0f

[10] Weisberg, E., Ayton, R., Darling, G., Farrell, E., Murkies, A., O'Neill, S., Kirkegard, Y., Fraser, I., 2005. Endometrial and vaginal effects of low-dose estradiol delivered by vaginal ring or vaginal tablet. Climacteric 8, 83–93. https://doi.org/10.1080/13697130500087016

Similarly, no endometrial stimulation with the use of 10 mcg vaginal estradiol cream daily for 3 weeks (followed by twice-weekly for 9 weeks) was observed by Santen and colleagues (2002) thickening of the endometrial stripe beyond 5 mm was noticed by ultrasound (Santen et al, 2002)[11].

Luisi and colleagues (1980) showed suppression FSH and LH by both, Premarin conjugated estrogen cream (1.25 mg conjugated equine estrogen (CEE)/day) and Ovestin estradiol cream (0.5 mg estradiol/day). The Premarin suppression was significantly greater than Ovestin. In contrast with Ovestin, Premarin caused moderate proliferation of the endometrium, observed in 2 patients and progressive rise in E1, E2 and sex-hormone binding globulins (SHBG) levels, Ovestin showed no changes (Luisi et al, 1980)[12].

Manonai and colleagues. described effective treatment of urogenital symptoms, restoration of normal vaginal epithelium reduction of vaginal pH during treatment by 25 mcg estradiol vaginal tablet or 1 g of CEE cream for 12 weeks (first 2 weeks daily, after that 10 weeks twice weekly). No significant differences in endometrial thickness was observed, however two case of endometrial proliferation was reported. No cases of mastalgia did not observed (Manonai, 2001)[13].

Abdominal discomfort, abdominal tenderness and muscle cramps was observed in 3 patients and one case of breast swelling after using of Premarin estradiol tablets 0.3 mg or 0.5 g of Premarin Vaginal cream cream (= 0.3 mg conjugated estrogens, 0.625 mg/g) for 14 days (Dorr, 2010)[7].

Martin demonstrated that delivery of estrogen into the peripheral circulation following vaginal application appears to be direct and anatomically similar to secretion of estrogen into the circulation by the ovary in case of treatment by Premarin conjugated estrogen cream (1.25 mg) and Estrace (0.2 mg of micronized estradiol) (Martin, 1979)[14].

Mettler and Olsen reported no severe adverse effects in case of treatment by 25 mcg estradiol vaginal tablets for 52 weeks (Mettler & Olsen, 1991)[15].

In summary of the available literature, no changes of the endometrial thickness were observed with use of vaginally applied estradiol products. Only non-severe adverse effect was reported, e.g. breast tenderness, hot flashes, headache and abdominal cramping, menses and backache, abdominal discomfort, abdominal tenderness and muscle cramps. Moreover, discharge, burning and sensation of cold was observed in case of Linoladiol cream. Conjugated estradiol cream Premarin (1.25 mg CEE) showed rapid suppression of the FSH, LH and rise of E1, E2 and SHBG and in 2 patients caused moderate proliferation of the endometrium. The literature overview did not reveal any new safety concerns, however there is still lack of information about safety of the medicinal products containing 0.01%w/w estradiol for topical use when used long-term.

Long-term safety data

As vaginal atrophy may be a chronic condition, the long-term use of treatment is an important question. Low-dose vaginal treatment does not increase risk of endometrial hyperplasia, in contrary to systemic estrogen-alone therapies (Lindahl, 2014)[16]. However, taking into account the systemic

[11] Santen, R.J., Pinkerton, J.V., Conaway, M., Ropka, M., Wisniewski, L., Demers, L., Klein, K.O., 2002. Treatment of urogenital atrophy with low-dose estradiol: preliminary results. Menopause N. Y. N 9, 179–187.
[12] Luisi, M., Franchi, F., Kicovic, P.M., 1980. A group-comparative study of effects of Ovestin cream versus Premarin cream in post-menopausal women with vaginal atrophy. Maturitas 2, 311–319.
[13] Manonai, J., Theppisai, U., Suthutvoravut, S., Udomsubpayakul, U., Chittacharoen, A., 2001. The effect of estradiol vaginal tablet and conjugated estrogen cream on urogenital symptoms in postmenopausal women: a comparative study. J. Obstet. Gynaecol. Res. 27, 255–260.
[14] Martin, P.L., Yen, S.S., Burnier, A.M., Hermann, H., 1979. Systemic absorption and sustained effects of vaginal estrogen creams. JAMA 242, 2699–2700.
[15] Mettler L., Olsen P.G. 1991.Long-term treatment of atrophic vaginitis with low-dose oestradiol vaginal tablets. Maturitas, 14 (1), pp. 23-31.
[16] Lindahl, S., 2014. Reviewing the options for local estrogen treatment of vaginal atrophy. Int. J. Womens Health 307. https://doi.org/10.2147/IJWH.S52555

absorption of high concentration estrogen cream, it cannot be compared with low-dose estrogen products, but rather with medium-dose ones. Therefore, its safety profile could not be considered as favourable as the one of low-dose estradiol products.

The first Cochrane review by Suckling and colleagues (2006) that focused on vaginally administered estradiol therapy such as creams, pessaries, tablets and estradiol-releasing rings in treatment of vaginal atrophy in menopausal women was published in 2006. In total 4162 women in 19 trials were included in the review. The results displayed evidence that the use of conjugated equine estrogen cream caused more incidents of vaginal bleeding than estrogen ring and another trial showed significant endometrial overstimulation following use of cream in comparison to vaginal ring (Suckling et al, 2006)[17].

Second Cochrane review by Lethaby and colleagues (2016) included 30 randomised controlled trials comparing intravaginal estrogenic preparations with one another or with placebo. The results showed that there was no convincing evidence of a difference in main adverse events (endometrial thickness, breast disorders or total adverse events) between estrogenic products versus each other or placebo. Unfortunately, most of the comparative trials were only small with high levels of uncertainty and huge diversity of treatment regimens, which cause difficulties in combining data in a meta-analyse. Review revealed a low-quality evidence that estrogen cream may be associated with an increase in endometrial thickness compared to estrogen ring. This is most probably caused due to higher doses of cream administered. Moreover, the low quality of evidence was caused by poor reporting of study methods and serious imprecision (Lethaby et al, 2016)[18].

In a multi-centre, randomised, double-blind parallel-group study 230 menopausal women were treated by 25 mcg and 10 mcg estradiol vaginal tablets. No significant changes in the endometrial thickness were observed. All endometrial thickness results were 5 mm or less. (Bachmann et al, 2008)[6].

Furthermore, in a study by Weisberg and colleagues (2005) where comparison of the ESTring (126 women) and estradiol vaginal tablet Vagifem (59 women) on vaginal symptoms was performed, no significant change in endometrial thickness over the first 12 weeks was observed in both groups. These low-dose estradiol products showed equivalent endometrial safety and efficacy ad relief of the symptoms of atrophic vaginitis (Weisberg et al, 2005)[10].

Santen discussed long-term treatment of vaginal estradiol administration of various dose preparations. In the low-dose estradiol preparations, during long-term use of e.g. Estring 7.5 mcg-silastic ring, values of estradiol levels remained under 20 pg/ml from days 14 to 84 (Holmgren et al, 1989)[19]. However, even though plasma levels of estradiol were below 20 pg/l with the low-dose preparations, systemic effects have been observed. Intermediate-dose estradiol preparations 25 mcg of vaginal estrogen showed that estradiol levels during chronic administration approached or exceeded the 20 pg/ml level. And finally, with high-dose estradiol preparations delivering 50-2000 mcg of estradiol, the levels in case of chronic use ranged from 35 to 200 pg/ml, that is similar to the early follicular and luteal phases of the menstrual cycle and thus considered systemic (Martin et al., 1984)[20].

Santen concluded that intermediate- and high-dose vaginal estradiol products are well absorbed and result in plasma levels approaching or exceeding premenopausal levels. Low doses also result in

[17] Suckling, J., Lethaby, A., Kennedy, R., 2006. Local oestrogen for vaginal atrophy in postmenopausal women. Cochrane Database Syst. Rev. CD001500. https://doi.org/10.1002/14651858.CD001500.pub2

[18] Lethaby, A., Ayeleke, R.O., Roberts, H., 2016. Local oestrogen for vaginal atrophy in postmenopausal women. Cochrane Database Syst. Rev. https://doi.org/10.1002/14651858.CD001500.pub3

[19] Holmgren, P.-Å., Lindskog, M., Schoultz, B. von, 1989. Vaginal rings for continuous low-dose release of oestradiol in the treatment of urogenital atrophy. Maturitas 11, 55–63. https://doi.org/10.1016/0378-5122(89)90120-5

[20] Martin, P.L., Greaney, M.O., Burnier, A.M., Brooks, P.M., Yen, S.S., Quigley, M.E., 1984. Estradiol, estrone, and gonadotropin levels after use of vaginal estradiol. Obstet. Gynecol. 63, 441–444.

absorption but estradiol levels during long-term administration are less than 20 pg/ml (Jameson & De Groot [21]; Santen, 2015[22]; Naumova & Castelo-Branco, 2018)[23].

The long-term exposition to medicinal products containing 100 mcg estradiol per 1g is not documented. The majority of existing studies focused on low-dose estradiol products which showed different characteristics than the higher-dosed estradiol products.

However, it is difficult to compare vaginal creams, vaginal tablets, vaginal rings, due to differences in dose and administration which may be daily, once or twice weekly, differences in initial administration and maintenance dose. Also, the composition of estrogens play major role in the absorption for example if the conjugated or micronized estradiol cream was applied. Moreover, serious issues in data interpretation may be caused by poor reporting of study methods and serious inaccuracy in the data.

These factors may have significant impact on the low-quality evidence obtained from various reviews presented in the latest Cochrane review by Lethaby and colleagues (Lethaby et al, 2016)[15], concerning association of estrogen vaginal creams with an increase in endometrial thickness. This is most probably caused due to higher doses of cream administered.

Overall, it can be concluded that there is a lack of long-term safety data concerning estradiol vaginal creams for topical use with higher estradiol concentration.

Concomitant use of progesterone

The addition of progestogen to the estrogen component is aimed to prevent endometrial hyperplasia and endometrial cancer risk associated with estrogen-only therapy for postmenopausal women with a uterus, as it is noticed in EMA Guideline on HRT ("EMEA/CHMP/021/97 Rev. 1," 2005). Various guidelines state that in postmenopausal women the upper normal limit of endometrial thickness ranges from 5 mm to 8 mm if the patient is on hormonal replacement therapy (Saksouk and Al-Kadhi, 2009[24]. When endometrial thickness is ≤5 mm, the risk of endometrial cancer is 0.07%, When the endometrial thickness is > 5 mm, the risk of endometrial cancer equals approximately 7.3%. In case no vaginal bleeding is reported, the risk of cancer is approximately 0.002% if the endometrium thickness is ≤ 11 mm and 6.7% if the endometrium is> 11 mm. (Smith-Bindman, 2004)[25].

According to North American Menopause Society (NAMS), the primary indication for progestogen is to reduce the risk of endometrial cancer in women with intact uterus on systemic estrogen therapy. In case of low-dose vaginal estrogen administration, generally there is no need for adding progestogens ("Management of symptomatic vulvovaginal atrophy," 2013).

Moreover, European Menopause and Andropause Society (EMAS) also suggested that there is no need to add a progestogen for endometrial protection when vaginally applied estrogens are used in the recommended doses, but the risk could be affected by the duration of treatment and the different preparations (Rees et al, 2012)[26].

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21 Jameson JL, De Groot LJ, n.d. Laboratory normal ranges. Endocriology: Adult and Pediatric, 6th edn. Philadelphia: Saunders. Philadelphia: Saunders.

22 Santen, R.J., 2015. Vaginal administration of estradiol: effects of dose, preparation and timing on plasma estradiol levels. Climacteric 18, 121–134. https://doi.org/10.3109/13697137.2014.947254

23 Naumova, I., Castelo-Branco, C., 2018. Current treatment options for postmenopausal vaginal atrophy; International Journal of Women's Health 10, 387-395. doi: 10.2147/IJWH.S158913

24 Faysal Saksouk, Al-Kadhi, Yusuf, A., n.d. http://www.emedicine. com/radio.htm Carcinoma, e-Medicine Specialties, Radiology, Obstetrics/gynecology. 2009

25 Smith-Bindman, R., 2004. How thick is too thick? When endometrial thickness should prompt biopsy in postmenopausal women without vaginal bleeding - Ultrasound in Obstetrics & Gynecology - Wiley Online Library [WWW Document]. URL https://obgyn.onlinelibrary.wiley.com/doi/full/10.1002/uog.1704 (accessed 6.19.19).

26 Rees, M., Pérez-López, F.R., Ceasu, I., Depypere, H., Erel, T., Lambrinoudaki, I., Schenck-Gustafsson, K., Simoncini, T., van der Schouw, Y.T., Tremollieres, F., 2012. EMAS clinical guide: Low-dose vaginal estrogens for postmenopausal vaginal atrophy. Maturitas 73, 171–174. https://doi.org/10.1016/j.maturitas.2012.06.009

Additionally, there are several updated recommendations decided by NAMS concerning adding of concomitant systemic progestogen. Firstly, for women with uterus using systemic estrogen, endometrial protection requires an adequate dose and duration of a progestogen or use of the combination CEE with bazedoxifene. Secondly, progestogen therapy is not recommended with low-dose vaginal estradiol, but appropriate evaluation of the endometrium should be performed if vaginal bleeding occurs ("The 2017 hormone therapy position statement of The North American Menopause Society," 2017).

The review by Lindahl mentions that progestogen is not generally indicated when vaginally applied estrogen products are used as low-dose vaginally administered estrogen has not been associated with increased risk of endometrial hyperplasia. However, there are no official recommendations in guidelines for adding progestogens to creams containing higher doses of estrogen (Lindahl, 2014)[14].

The addition of progestogen will reduce the risk of endometrial carcinoma, presumably by reducing estrogen-receptor concentration and increasing estradiol dehydrogenase activity (Korenman, 1982)[27]. Even low-dose therapies should be opposed by occasional progestogen to prevent endometrial carcinoma (Ballagh, 2005)[28].

Martindale, too advises that in women with a uterus, a progestogen is required, given cyclically or continuously, usually by mouth although some combined transdermal preparations are available (Brayfield, 2014)[29].

One recommendation provided by Cochrane review showed the need of additional progestogenic protection in women with uterus using vaginally applied conjugated equine estrogen cream if the dose used results in systemic estrogen absorption (usually doses of conjugated estrogens greater than 0.5 mg/daily) (Suckling et al, 2006)[17].

It is expected, that the risk associated with the estrogen treatment will increase with the treatment prolongation. Based on the official guidelines such as NAMS, EMAS and others. there is no need for adding concomitant progestogen in case of low-dose vaginal estrogen preparations because the risk of endometrial hyperplasia or carcinoma is not expected. However, endometrial safety data beyond 1 year treatment are lacking.

Moreover, there are no official guidance recommendations for adding progesterone in case of intermediate- or higher-dose estradiol in the vaginal medicinal products especially in the context with long-term exposition.

Conclusions on the safety of high dose oestrogen products

Based on EudraVigilance search 37 cases reporting ADRs after topical application of estradiol cream in concentration of 100mcg/g were detected. In these 37 individual cases 148 reactions were described. 27 out of 37 cases described serious reactions. 14 cases reported main risks known to be associated with the use of estradiol in systemic HRT (breast cancer, cerebrovascular accidents and endometrial thickening), but in 13 of these cases systemic HRT was used concomitantly. In 6 of these cases a long-term use of high concentration estradiol cream was described. A potential additive effect of estradiol vaginal cream to HRT associated risks cannot be ruled out.

Sixteen other cases out of all 37 described reactions which are listed for estradiol products for systemic use, such as breast pain, headache, alopecia, muscle spasm, dizziness, nausea, mood swings,

[27] Korenman SG. 1982. Menopausal endocrinology and management. Arch Intern Med; 142:1131-1136
[28] Ballagh, S.A., 2005. Vaginal hormone therapy for urogenital and menopausal symptoms. Semin. Reprod. Med. 23, 126–140. https://doi.org/10.1055/s-2005-869480
[29] Brayfield A., ed. Sex Hormones and their Modulators. Estradiol. In: Martindale: The Complete Drug Reference. 38th edition. London: Pharmaceutical Press; 2014. p.2271-4

abdominal pain and arthralgia. Five of these cases were serious. In 11 out of 16 cases no concomitant HRT use was reported.

Majority of all case reports have several confounders, therefore no clear proof of systemic ADRs related only to medicinal products containing 100mcg estradiol per 1g for intravaginal use can be demonstrated. However due to known underreporting especially for topical products, and due to 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 data, given the scarcity of data, definite conclusions on the safety of medicinal products containing 100mcg estradiol per 1g in the post-marketing setting cannot be drawn.

Cases indicative of long-term use reported the range of the treatment duration from 6 weeks to 5 years, which in the light of missing systematically collected long-term data raises reasonable suspicion about the safe use of high estradiol concentration medicinal products.

Whilst it is acknowledged that available post-marketing safety data do not bring sufficient evidence on potential causal relationship between long-term use of 0.01w/w topical estradiol and estrogen associated risks (breast and ovarian cancer, endometrial hyperplasia and carcinoma and thromboembolic events), limitations of the spontaneous reporting in the identification of ADRs with prolonged TTO clinical manifestation (oncological disease) needs to be considered and the absence of the evidence is not considered sufficient for the recommendation of the treatment duration longer than 4 weeks.

Safety data from literature are extremely scarce. Regarding estradiol cream in concentration of 100mcg/g there exists only 1 study which identified 83 non-serious ADRs in 29 patients from total of 51 patients treated. However, this study's duration was only for 4 weeks.

In published literature, no changes of the endometrial thickness were observed with the use of vaginally applied estradiol products such as vaginal creams, vaginal tablets. Only non-severe adverse effects were reported, e.g. breast tenderness, hot flashes, headache and abdominal cramping, menses and backache, abdominal discomfort, abdominal tenderness and muscle cramps. Moreover, discharge, burning and sensation of cold was observed in case of Linoladiol cream. Conjugated estradiol cream (Premarin; 1.25 mg conjugated estradiol per day) showed rapid suppression of the FSH, LH and rise of estrone (E1), estradiol (E2), and sex hormone binding globulin (SHBG) and in 2 patients caused moderate proliferation of the endometrium.

The long-term exposure to medicinal products containing 100 mcg estradiol per 1g is not documented. The majority of existing studies focused on low-dose estradiol products which showed different characteristics than the higher-dosed estradiol products.

However, it is to be noted that it is difficult to compare vaginal creams, vaginal tablets, vaginal rings, due to differences in dose and administration which may be daily, once or twice weekly, differences in initial administration and maintenance dose. Also, the composition of estrogens play major role in the absorption for example if the conjugated or micronized estradiol cream was applied. Moreover, serious issues in data interpretation may be caused by poor reporting of study methods and serious inaccuracy in the data. These factors may have significant impact on the low-quality evidence obtained from various reviews presented in the latest Cochrane review (Lethaby et al., 2016)[14], concerning association of estrogen vaginal creams with an increase in endometrial thickness. This is most probably caused due to higher doses of cream administered.

Overall, although the case reports and the literature review did not reveal any new safety concerns there is still lack of safety information of medicinal products containing 0.01% w/w estradiol for topical use when used long-term.

3. Expert consultation

The PRAC in order to get more information on the clinical use of this group of products consulted a group of experts in gynaecology including representatives on women health.

First and foremost the PRAC wanted to discuss the therapeutic place in clinical practice of high-strength estradiol-containing creams, for the treatment of symptoms of vaginal atrophy due to oestrogen deficiency in postmenopausal women, compared to low-strength estradiol containing topical products.

The experts agreed that the topical use of high-strength may not be considered as first line treatment. They also added that low-dose preparations may be used, often for a limited time, after which the condition may resolve satisfactorily or require a new treatment cycle, or as long-term treatment from the beginning. Some experts also might consider a high dose topical product for a short period followed by maintenance treatment with a low dose product. However, the experts pointed out that there is only one 4-week study on their use, as well as lack of information in the literature.

Moreover, estimation of a clinical benefit of high-dose products is further hindered by the weak correlation between the use of local oestrogen-preparations, compared to placebo or lubricants, and symptom relief.

The experts noted that cases of adverse drug reactions identified in a EudraVigilance search were associated with a high prevalence of long-term use from 6 weeks to 5 years as well as concomitant to HRT. To prevent this, a further strengthening of both the SmPC as well as the product patient leaflet was urged by the experts, including the patient representatives.

The consumer representatives pointed out that the relevance and consequence of topical use of a "high dose" vs. a "low dose" product may not be sufficiently clear. As the local application of a high-dose product may be expected to result in systemic exposure levels exceeding normal post-menopausal levels, and their possibly associated risks, this should be clearer from the information provided to the patients. Moreover, they highlighted that for patients to differentiate a "high dose" from a "low dose" product may not be straight-forward.

Some experts and patients' representatives highlighted that the description of the product's strength in microgram/gram may make this not sufficiently obvious for the prescriber and/or user. Besides adequate patient information, one patient representative emphasised that a part of the target patient population is expected to rely largely on healthcare professionals' advice, which should also be as clear as possible.

Overall, the experts agreed that the topical use of high-strength estradiol-containing products for treatment of vaginal atrophy in postmenopausal women, if considered at all, is seen as a limited second line therapeutic option, with uncertain benefits and risks compared to low-dose products.

The PRAC wanted also to discuss with the experts the clinical practice regarding the duration of topical treatment of vaginal atrophy due to estrogen deficiency in postmenopausal women, with estradiol 0.01% w/w cream.

The duration of use of low dose oestrogen products for vaginal application may vary somewhat in different EU member states/practices: In some, treatment for 8-10 weeks is common, with restart of treatment e.g. 3 months later, if needed. In others, longer-term, continuous treatment seems more

common. Some experts prefer long-term use, *a priory* as symptoms often may recur, and also often combined with systemic treatment.

The experts agreed that the product should not be used repetitively due to the lack of long-term data.

Overall, the experts agreed that the use of these high-dose preparations with topical application, if indicated at all, should be limited to maximum of 4 weeks under any circumstances, in particular considering the systemic exposure levels reached and the very limited data available regarding the safety profile of longer-term use of such product.

4. Benefit-risk balance

4.1. Initial benefit-risk balance assessment

The products subject to this procedure are used in topical applications to relieve symptoms of vaginal atrophy in postmenopausal women.

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 mcg estradiol per g.

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.

Indeed, a significant increase to five times above the upper limit of the reference postmenopausal estradiol serum levels of 10-20 pg/mL and also the increase above the upper reference limit of 50 pg/mL implies that medicinal products containing 0.01% w/w estradiol for topical use should be seen as medicinal products for which possible risks due to systemic exposure apply.

Whilst no dose-finding studies have been performed and despite the limited data as 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.

Based on the Eudravigilance search, cases reporting ADRs after topical application of estradiol cream in concentration of 100mcg/g were detected.

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), although in some of these cases systemic HRT was used concomitantly. In other of these cases a long-term use of high concentration estradiol cream was described. A potential additive effect of estradiol vaginal cream to HRT associated risks could not be ruled out.

Although the majority of all case reports have several confounders, no clear proof of systemic ADRs related only to medicinal products containing 100mcg estradiol per g for intravaginal use can be demonstrated. Due to known underreporting especially for topical products, and due to 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 data given the scarcity of data, 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.

In addition, cases indicative of long-term use reported the range of the treatment duration from 6 weeks to 5 years, which in the light of missing systematically collected long-term data raises reasonable suspicion about the safe use of high estradiol concentration medicinal products.

Safety data from literature is extremely scarce. The only study which identified 83 non-serious ADRs in 29 patients from total of 51 patients treated had duration only 4 weeks.

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 concerns 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 on the duration of their use in view that vaginal atrophy is a long-term condition. 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 products. In addition the experts agreed 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.

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

Hence, the PRAC taking all the available data into account requested that the contraindications and warnings are 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 risks of thromboembolism events, breast and endometrial cancer. 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.

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.

In view of the above, the Committee considers that the benefit-risk balance of estradiol-containing (0.01% w/w) medicinal products for topical use remains favourable subject to the agreed changes to the marketing authorisations, and taking into account the agreed amendments to the product information and other risk minimisation measures.

4.2. Re-examination procedure

Following the adoption of the PRAC recommendation in October 2019, one MAH (Dr. August Wolff GmbH & Co. KG Arzneimittel) requested the re-examination of the recommendation on 23 October 2019and submitted detailed grounds for the re-examination on 9 December 2019. It is noted that the PRAC is a scientific committee and that, while PRAC operates within the framework of the Union legislation regulating medicinal products, it cannot discuss the specific merits of procedural and legal aspects of administrative procedures laid down in the legislation. As a result, procedural and legal considerations are outside the remit of the PRAC, and therefore the re-examination of the PRAC initial recommendation, adopted in the framework of the referral procedure under Article 31 of Directive 2001/83/EC resulting from pharmacovigilance data, focuses only on the scientific grounds for re-examination.

4.2.1. Detailed grounds for re-examination submitted by the MAH August Wolff GmbH & Co. KG Arzneimittel

In this section the detailed grounds of the MAH are presented as submitted on 9 December 2019.

i. Conclusions drawn from pharmacokinetic study data provided (study report SCO 5109)

The MAH conducted a pharmacokinetic study (cf. study report SCO 5109) which has already been provided in the previous communication regarding the present Referral under Art. 31 of Directive 2001/83/EC.

In the final assessment report as of 10 October 2019, the PRAC presented the following overview of pharmacokinetic data:

"The results for estradiol were as follows:

- mean (SD) AUC_{0-36}: 1285.2 (362.1) pg/mL·h
- mean (SD) C_{max}: 103.5 (37.7) pg/mL
- mean t_{max}: 6.81 hours
- mean (SD) concentration at 24 h: 14.5 (7.2) pglmL
- mean (SD) concentration at 36 h (C_{min}): 10.7 (3.9) pglmL
- average serum concentration: 33 pglmL (calculated for a dosage interval of 24 hours, predicted under the assumption of linear PK)."
-

Furthermore, after assessing the overall data provided in the above-mentioned study, the PRAC concluded the following outcome:

> *"Although there is only data of a single dose full PK study available, when looking at the C_{max} of 103.*5 *pg/mL estradiol, a significant increase to five times above the upper limit of the reference postmenopausal estradiol serum levels of 10-20 pglmL but also above the upper reference limit of* 50 *pg/mL has been observed after vaginal application of a single-dose Linoladiol N cream.*

Also, the calculated average serum concentration for a dosage interval of 24 hours ($C_{average}$) of 33 pglmL lies substantially above the reference range of 10-20 pglmL, which is of concern. Systemic effects due to vaginal absorption of estradiol after use of Linoladiol N cream can therefore be expected."

Dr. August Wolff GmbH & Co. KG Arzneimittel acknowledges the tabulated overview of the pharmacokinetic parameters (AUC_{0-36}, C_{max}, t_{max} and C_{min}) and is aware that the determined mean maximum estradiol level (C_{max}) of 103.5 pg/ml not only exceeds the upper limit of the reference postmenopausal estradiol serum levels of 10-20 pg/ml but also the upper reference limit of 50 pg/ml.

However, deriving an average serum concentration ($C_{average}$) for a dosage interval of 24 hours of 33 pg/ml does not appear to be sensible since the actual dosage interval for Linoladiol N is 48 hours (during the first week of treatment) and 72 to 96 hours (during week 2 to 4), respectively. Therefore, the basis for the calculation of the above-mentioned average serum concentration ($C_{average}$) after single application of Linoladiol N is not comprehensible and requires further explanation.

It should also be emphasized that the described elevated estradiol serum levels after absorption are temporary with respective estradiol concentrations dropping to baseline values approximately 36 hours after application (cf. Figure 1). Given the Linoladiol N dosage interval of 48 hours (week 1) and 72 to 96 hours (week 2 to 4), respectively, build-up of an estradiol steady-state not to be expected; thus a potential risk originating from absorbed estradiol is to be assessed less pronounced as compared to systemic HRT products such as tablets, patches or transdermal gels which are used over a prolonged period of time with the intention to build-up an estradiol steady state above the normal post-menopausal range.

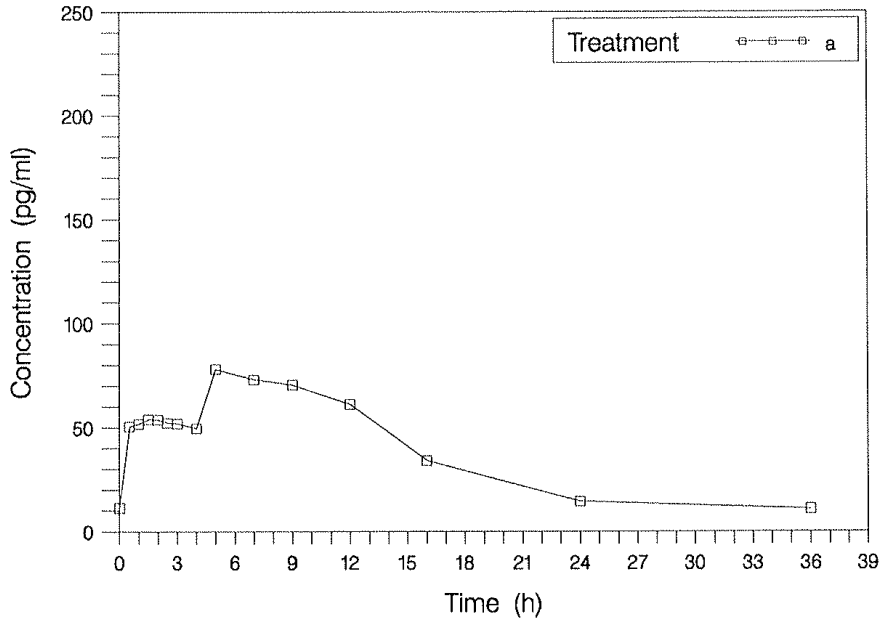

Figure 1: Estradiol mean serum concentrations after single application of Linoladiol N.

In our opinion, the conclusions drawn by the PRAC are believed to be insufficient in order to justify the requested limitation of use of estradiol-containing (0.01% w/w) medicinal products for topical use to a single treatment period up to 4 weeks maximum; thus a re-evaluation of the relevance of temporarily elevated estradiol levels with regard to the resulting risk profile under consideration of a proposed treatment duration of 4 weeks should be performed by the PRAC.

ii. Feasibility of the core product information on HRT products under consideration of the risk minimisation measures as proposed by the PRAC

As substantiated in the final assessment report as of 10 October 2019, the PRAC requested the product information to be updated in accordance with the Core SmPC for HRT elements for estrogen products for vaginal application of which the systemic exposure to the estrogen is higher than the normal post-menopausal range. At the same time, several risk minimisation measures were recommended including, amongst others, limitation of use of estradiol-containing (0.01% w/w) medicinal products for topical use to a single treatment period up to 4 weeks.

Whilst Dr. August Wolff GmbH & Co. KG Arzneimittel generally acknowledges the necessity of comparable product information texts, the similarity of estradiol-containing (0.01% w/w) medicinal products for topical use as compared to systemic HRT products such as tablets, patches and transdermal gels is limited.

Even though individual pharmacokinetic parameters such as C_{max} may be in the same range for both above mentioned product types, major differences for other PK parameters may be present, making clustering of the HRT products with different routes of administration different dosage regimens implausible.

For example, build-up of high estradiol levels at steady-state is particularly intended in case of systemic HRT products such as tablets, patches or transdermal gels but highly unlikely to occur following application of estradiol-containing (0.01% w/w) medicinal products for topical use given the dosage interval of 48 hours (week 1) and 72 to 96 hours (week 2 to 4), respectively. In consequence, steady-state estradiol levels in the range of 60 to 80 pg/ml are observed after application of estradiol-containing transdermal gels (Gynokadin Dosiergel) or after oral administration of estradiol-containing tablets (Femoston mono 2 mg) but are not expected after application Linoladiol N.

The above mentioned, differences in product properties may lead to different pharmacokinetic profiles which can have an impact on the feasibility of adaption of the core product information on HRT products under consideration of the risk minimisation measures as requested by the PRAC. For example, a restriction of estradiol-containing (0.01% w/w) medicinal products for topical use to a single treatment period of maximum 4 weeks is incompatible with the information provided in section 4.8 ("Undesirable effects") of the core SmPC for hormone replacement therapy products as of February 2017 which relates to risks (e.g. for development of breast cancer) following combined or oestrogen-only HRT over a 5-year period.

In the opinion of Dr. August Wolff GmbH & Co. KG Arzneimittel, a rational re-examination of the feasibility of adoption of the core product information on HRT products under consideration of the risk minimisation measures as proposed by the PRAC should be performed.

iii. Proportionality of the risk minimisation measures as proposed by the PRAC in context of the available body of data

Regarding the proposed amendments of the product information, Dr. August Wolff GmbH & Co. KG Arzneimittel agrees to most adjustments as suggested by the PRAC except for the re- quested restriction of estradiol-containing (0.01% w/w) medicinal products for topical use to a single treatment cycle of 4 weeks.

Based on the PRAC assessment report as of 10 October 2019, the restriction of repeated use is justified by a lack of long-term safety data as well as missing safety data following repeated use and the systemic estradiol exposure after application of estradiol-containing (0.01% w/w) medicinal products for topical use above the normal postmenopausal range:

"The PRAC noted that data on long-term treatment as well as repeated use of estradiol-containing (0.01% wlw) medicinal products for topical use is not available. Given the systemic exposure above normal postmenopausal range, these products should only be used for a single treatment period up to 4 weeks maximum."

In the opinion of Dr. August Wolff GmbH & Co. KG Arzneimittel, considering the lack of long-term safety data with estradiol-containing (0.01% w/w) medicinal products for topical use, a limitation of the use to maximum of 4 weeks is an appropriate measure to minimise potential risks from long-term use of these products.

However, a further restriction to a single treatment period of 4 weeks is considered as disproportionate and insufficiently justified. As previously acknowledged, estradiol levels above the normal postmenopausal range were determined after single application of Linoladiol N; however, the observed elevated estradiol levels are temporary and rapidly drop to baseline concentrations approximately 36 hours after application. Given the dosage interval of 48 hours (week 1) and 72 to 96 hours (week 2 to 4), respectively, build-up of steady- state estradiol levels during a 4-week treatment cycle is not to be expected.

In consequence, the risk of undesired effects due to estradiol levels above the normal postmenopausal range after application of estradiol-containing (0.01% w/w) medicinal products for topical use is to be assessed as less pronounced as compared to systemic HRT products such as tablets, patches or transdermal gels which are known to exhibit high steady-state estradiol levels and which are commonly used over a prolonged period of time.

Taking into account that the currently proposed risk minimisation measures for estradiol-containing (0.01% w/w) medicinal products for topical use exceed the warning and precautious measures proposed for long-term use of systemic HRT products, the justification provided by the PRAC for the proposed restriction of estradiol-containing (0.01% w/w) medicinal products for topical use to a single treatment period of 4 weeks is incomprehensible and requires further clarification, especially considering the already agreed limitation of the treatment duration of 4 weeks as compared to conventional HRT products which can be used over a prolonged period of time (e.g. several years).

It should also be emphasized that the previously outlined disproportionality of a restriction of estradiol-containing (0.01% w/w) medicinal products for topical use to a single treatment period of 4 weeks is not considered for similar products which are available in other countries. For example, despite an overall comparable body of published safety data of estradiol-containing (0.01% w/w) medicinal products for topical use, a respective limitation is not required for the FDA-approved medicinal product "Estrace Cream" (estradiol vaginal cream, 0.01%, USP) which is currently marketed in the United States.

In the opinion of the MAH, restriction of estradiol-containing (0.01% w/w) medicinal products for topical use to a single treatment period of 4 weeks should further be justified by the PRAC.

4.2.2. PRAC discussion on grounds for re-examination

The MAH Dr. August Wolff GmbH & Co. KG Arzneimittel (hereinafter 'the MAH') submitted detailed grounds and presented arguments on the conclusions drawn on the pharmacokinetic study provided (study SCO 5109), on the feasibility of the core product information of HRT products under consideration of the risk minimisation measures as proposed by PRAC and on the proportionality of the risk minimisation measures in context of the available body of data.

i. Conclusions drawn from pharmacokinetic study data provided (study report SCO 5109)

According to the first MAH ground raised, the MAHconsidered that the data from the PK study were insufficient to lead to the PRAC conclusion that the use of the products should be limited to 4 weeks.

The MAH questioned the relevance of the average serum concentration ($C_{average}$) of 33 pg/ml, derived from a dosage interval of 24 hours for risk assessment associated with the systemic exposure of the concerned medicinal products since the actual dosage interval for Linoladiol N is 48 hours (during the first week of treatment) and 72 to 96 hours (during week 2 to 4), respectively. The MAH also emphasised that the described elevated estradiol serum levels after absorption are temporary, with respective estradiol concentrations dropping to baseline values approximately 36 hours after application and a build-up of an estradiol 'steady-state' is not to be expected when used according to the proposed dosage interval. Based on this, the MAH is of the opinion that a potential risk originating from absorbed estradiol should be assessed less pronounced as compared to systemic HRT products, which are used over a prolonged period of time with the intention to build-up an estradiol steady state above the normal post-menopausal range.

This PK study (SCO 5109) was submitted by the MAH and was considered relevant by the PRAC to evaluate the extent of the systemic absorption after single administration of estradiol-containing (0.01% w/w) medicinal products for topical use.

These data are relevant as it showed a significant and concerning systemic absorption after single administration of these products.

Although the dosing during the first week of treatment is 2 grams of cream every 48 hours, only the PK data for the first 36 hours after dosing are available. PRAC considered the $C_{average}$ of 33 pg/ml concentration after 24 hours relevant as it serves as a basis in the scope of risk assessment.

Furthermore, the PRAC did not solely take into consideration the $C_{average}$ for 24 hours regarding the provided PK study, but the totality of PK data. When looking at the C_{max} of 103.5 pg/mL of estradiol, a significant 5-fold increase above the upper limit of the reference postmenopausal estradiol serum levels of 10-20 pg/mL but also above the upper reference limit of 50 pg/mL has been observed after vaginal application of a single-dose of Linoladiol N.

Furthermore, serum levels above 20 pg/mL can be observed up to at least 20 hours after a single application. The provided PK data (C_{max}, elevated estradiol levels over several hours) after vaginal application of Linoladiol N evidences a repeatedly significant systemic exposure to estradiol. The vaginal application after a single administration of estradiol-containing (0.01% w/w) medicinal products for topical use, leads to systemic exposure above the normal postmenopausal range which raises serious doubts on the safety risks associated with systemic exposure to estradiol of these medicinal products when used *as per* the conditions of use in the product information.

The PRAC took into consideration that a 24 hours dosing interval does not reflect the dosing recommendations in the product information of Linoladiol N (48 hours (during the first week of treatment) and 72 to 96 hours (during week 2 to 4)) and that this elevated levels are temporary and return to the initial levels after 36 hours. The PRAC noted that the MAH infers from this that the build-up of an estradiol 'steady-state' is not to be expected when used according to the proposed dosage interval and that a potential risk originating from absorbed estradiol should be assessed less pronounced as compared to systemic HRT products, which are used over a prolonged period of time with the intention to build-up an estradiol steady-state above the normal post-menopausal range.

The PRAC disagreed with these arguments. Firstly, the safety concern at stake is not that the risk is higher or lower than systemic HRT products but that the topical treatment with these products leads to systemic exposure and therefore, exposes the patients to associated adverse reactions. The arguments

that the increase is temporary or that a 'steady-state' continuously above the normal postmenopausal range is not achieved does not refute that those patients are exposed to systemic levels of estradiol above the normal postmenopausal range which is the safety concern at stake. On the contrary, the systemic absorption observed after vaginal application of a single-dose Linoladiol N is high (C_{max} of 103.5 pg/mL estradiol, a significant 5-fold increase above the upper limit of the reference postmenopausal estradiol serum levels of 10-20 pg/mL but also above the upper reference limit of 50 pg/mL) reaching levels comparable to systemic HRT products. Moreover, this systemic exposure above the normal postmenopausal range lasts for 36 hours to estradiol which, contrary to MAH's claim, is not a rapid decrease. The extent and duration of this systemic exposure is of concern for a treatment that is intended to act locally and raise serious doubts on the safety of estradiol-containing (0.01% w/w) medicinal products for topical use. Secondly, it should be taken into account that estradiol-containing (0.01% w/w) medicinal products for topical use are intended to act locally to treat a local condition (vaginal atrophy due to estrogen deficiency in post-menopausal women), on the contrary of HRT systemic products that are intended to act systemically. Therefore, whilst for HRT systemic products a certain level of systemic absorption is the goal of the treatment, on the contrary for estradiol-containing (0.01% w/w) medicinal products for topical use, systemic absorption is not intended (and is rather an undesirable effect) as it would expose patients to adverse reactions that are not acceptable in view of the authorised indication (topical treatment of vaginal atrophy).

As acknowledged by the MAH in its grounds, the restriction to a treatment up to 4 weeks is justified in view of the systemic exposure to estradiol after topical application. This systemic exposure as well as the lack of safety data for prolonged or repeated courses of 4 weeks raise serious doubts on the safety of these products beyond 4 weeks or repeated treatment. In particular, it is of concern that every additional treatment cycle could increase the risk of proliferative changes to the endometrium.

Therefore, in view of these serious doubts on the safety of estradiol-containing (0.01% w/w) medicinal products for topical use, the PRAC considered that the use of these medicinal products should be restricted to a single treatment up to 4 weeks.

ii. Feasibility of the core product information on HRT products under consideration of the risk minimisation measures as proposed by the PRAC

Whilst the MAH generally acknowledged the necessity of comparable product information wording, they considered that the similarity of estradiol-containing (0.01% w/w) medicinal products for topical use as compared to systemic HRT products such as tablets, patches and transdermal gels is limited, and that major differences for other PK parameters may be present, making clustering of the HRT products with different routes of administration and different dosage regimens implausible.

The MAH also argued that differences in product properties may lead to different pharmacokinetic profiles which can have an impact on the feasibility of adaption of the core product information on HRT products under consideration of the risk minimisation measures as requested by the PRAC.

In the opinion of the MAH, a rational examination of the applicability of adoption of the core product information on HRT products in consideration of the risk minimisation measures should be performed.

As mentioned in the evaluation of the first ground, the HRT systemic products cannot be used as direct comparison with topical products. Indeed, the safety concern at stake is not whether there is a higher or lower risk with estradiol-containing (0.01% w/w) medicinal products for topical use compared to HRT systemic products, but the fact that there is a systemic exposure above normal postmenopausal range after a single application of estradiol-containing (0.01% w/w) medicinal products for topical use. The safety risk of adverse reactions associated with a systemic exposure to estradiol can not be excluded based on available safety data. Topical treatments containing estradiol are intended for use to avoid the adverse reactions associated with HRT systemic products (e.g. oral or transdermal

products) – therefore systemic exposure above the menopausal levels to estradiol for these products is of concern, and the associated risks (e.g. risk of venous thromboembolisms, stroke, ovarian cancer endometrial carcinoma) are not proportionate to the indented use (i.e. a local condition – topical treatment of vaginal atrophy).

In addition to the MAH's arguments, the PRAC also found not relevant the comparison with lower concentration estradiol containing products for topical use which either do not lead to systemic exposure to estradiol or for which the systemic exposure is not above the normal postmenopausal range.

Whilst the MAH claimed that different estradiol-containing products may have major PK differences, they did not establish if and how these differences would translate in clinical practice. The MAH submitted only data for a single treatment up to 4 weeks and did not establish that the treatment would be safe for a prolonged or repeated 4-week courses of treatment. On the contrary, the systemic exposure above normal postmenopausal range after a single application of these products raise serious doubts on their safety beyond 4 weeks or in case of repeated treatments.

In view of this systemic exposure above normal postmenopausal range, the PRAC therefore confirmed that it is appropriate as a risk minimisation measure to update the product information in accordance with the the principles stated in the Core product information for HRT elements for estrogen products for vaginal application of which the systemic exposure to the estrogen is higher than the normal postmenopausal range.

The PRAC carefully reviewed and confirmed that all statements in the product information recommended by the PRAC as a result of this referral procedure (Attachment 1 to this report) are relevant for estradiol-containing (0.01% w/w) medicinal products for topical use. Where appropriate, description on the class effects associated with systemic exposure to estradiol were provided.

Whilst information might in some cases be drawn from other forms such as oral or transdermal products, the PRAC confirmed that in the absence of appropriate safety data and in view of the systemic exposure to estradiol after a single administration of estradiol-containing (0.01% w/w) medicinal products for topical use, excluding these risks from the product information is not scientifically justified and would prevent minimisation of the risk by the healthcare professionals and the patients.

Providing all information, including undesirable effects associated with systemic exposure to estradiol irrespective of the pharmaceutical form, is important in view of the systemic exposure to estradiol above normal postmenopausal range after a single administration estradiol-containing (0.01% w/w) medicinal products for topical use. This information is needed for the healthcare professionals in order to make the most informed decision in prescribing and for the patients in order to be aware and be able to detect any symptoms in relation with these undesirable effects. In addition, the awareness of these safety risks is important as patients might have received before or might receive after this treatment other estradiol-containing medicinal products leading to a systemic exposure, which needs to be taken in evaluating the cumulative exposure and the benefit/risk balance for each patient.

To this effect it should be noted that in the experts meeting organised during this procedure, the patient representatives stated that further awareness on the fact that the local application of a high-dose product may be expected to result in systemic exposure levels exceeding normal post-menopausal levels and their possibly associated risks, should be clear in the information provided to the patients.

In conclusion, the PRAC confirmed that the statements in the product information (Attachment 1 to this report) are appropriate.

iii. Proportionality of the risk minimisation measures as proposed by the PRAC in context of the available body of data

Regarding the proposed amendments to the product information, the MAH did not accept the restriction medicinal products containing estradiol 0.01% w/w for topical use to a single treatment cycle of 4 weeks.

In MAH's view, considering the lack of long-term safety data with medicinal products containing estradiol 0.01% w/w for topical use, a limitation of the use to maximum of 4 weeks is an appropriate measure to minimise potential risks from long-term use of these products. A further restriction to a single treatment period of 4 weeks is considered as disproportionate and insufficiently justified, according to the MAH. In their view, estradiol levels above the normal postmenopausal range were determined after single application of Linoladiol N; however, according to the MAH the observed elevated estradiol levels are temporary and rapidly drop to baseline concentrations approximately 36 hours after application. Given the dosage interval of 48 hours (week 1) and 72 to 96 hours (week 2 to 4), respectively, build-up of steady- state estradiol levels during a 4-week treatment cycle is not to be expected. In consequence, the risk of undesired effects due to estradiol levels above the normal postmenopausal range after application of medicinal products containing estradiol 0.01% w/w for topical use should be assessed as less pronounced as compared to systemic HRT products such as tablets, patches or transdermal gels which are known to exhibit high steady-state estradiol levels and which are commonly used over a prolonged period of time. In the opinion of the MAH, restriction of medicinal products containing estradiol 0.01% w/w for topical use to a single treatment period of 4 weeks should further be justified by the PRAC.

As detailed in the evaluation of the first detailed ground, the PRAC concluded that the data from the available PK study (SCO 5109) show a systemic exposure after a single topical application of medicinal products containing estradiol 0.01% w/w. Despite that the elevated estradiol levels can only be measured temporarily and return to the baseline value after 36 hours, this finding is of serious concern. The systemic absorption observed after a single vaginal application of a single-dose of Linoladiol N is high (C_{max} of 103.5 pg/mL estradiol, a significant 5-fold increase above the upper limit of the reference postmenopausal estradiol serum levels of 10-20 pg/mL but also above the upper reference limit of 50 pg/mL). Moreover, this systemic exposure above the normal postmenopausal range lasts for 36 hours to estradiol which, contrary to MAH's claim, is not a rapid decrease. Due to the lack of long-term safety studies (especially on endometrial safety); the extent and duration of the systemic exposure is of concern for a treatment that is intended to act locally and raise serious doubts on the safety of estradiol-containing (0.01% w/w) medicinal products for topical use since the adverse reactions associated with a systemic exposure to estradiol cannot be excluded based on the available safety data. Other elements, such as the dosing intervals or the comparison to other products are not relevant and have been discussed in detail in the previous grounds.

In view of these safety risks, risk minimisation measures are warranted.

Whilst the MAH agreed that the use of these medicinal products should be restricted to a maximum of 4 weeks, the MAH disagreed with the PRAC conclusions that the treatment could not be prolonged or repeated.

The PRAC considered measures to minimise the risks to expose unduly patients to potential safety risks associated with systemic exposure to estradiol. Data provided supported an efficacious and safe use for a single treatment up to 4 weeks; no long-term or repeated-use data have been provided that would support a use beyond 4 weeks or repeated courses of treatment. The PRAC took into consideration that estradiol-containing (0.01% w/w) medicinal products for topical use are intended to act locally to treat a local condition (vaginal atrophy) and therefore the risk of undesirable effects associated with a systemic exposure to estradiol is not proportionate to the benefits. The PRAC

therefore rejected the MAH's proposal in view of the serious doubts on the safety risks of estradiol-containing (0.01% w/w) medicinal products for topical use beyond a single treatment of 4 weeks. In addition, no data were also provided to establish the efficacy of estradiol-containing (0.01% w/w) medicinal products for topical use in these settings. It was also considered by the PRAC that an increase in oestrogen-related risk with repeated use of these products cannot be ruled out and is therefore a safety concern. Without further characterisation of the safety risks beyond 4 weeks or in case of repeated treatment, the PRAC considered that patients should not be exposed to these risks.

Additionally, reference was made by the MAH to a medicinal product authorised in the USA, Estrace Cream (0.01% estradiol vaginal cream), for which treatment duration is not limited to one 4-week treatment period. Without the need to evaluate differences in clinical practices between US and EU, as well as the data that was submitted in support of the Estrace product information (in particular long-term safety data), the PRAC considered this reference not relevant for the present referral procedure as this medicinal product may be used together with a progestogen according to the product information. Whilst concomitant prescription with a progestogen can reduce the risk of some undesirable effects associated with estrogen, the estrogen-progestogen combination raises other safety concerns (e.g. breast cancer). In view of this difference, no extrapolation can be made on the safety of long-term use of estradiol-containing (0.01% w/w) medicinal products for topical use that is not to be prescribed with a concomitant progestogen.

The PRAC consulted experts in gynaecology during this referral procedure in order to better understand the therapeutic place of these high-dose products for the treatment of symptoms of vaginal atrophy due to oestrogen deficiency in postmenopausal women. Overall, the experts were of the view that the topical use of high-dose estradiol-containing products in this indication, if considered at all, is seen as a limited second line therapeutic option, with uncertain benefits and risks compared to low-dose products. The experts also concurred that these products should not be used repetitively due to the lack of long-term data and that, if indicated at all, their use should be limited to a maximum of 4 weeks under any circumstances, in particular considering the systemic exposure levels reached and the very limited data available regarding the safety profile of longer-term use of such product. The patient representatives stated that further awareness that the local application of a high-dose product can result in systemic exposure levels exceeding normal post-menopausal levels and their possibly associated risks, should be clearer from the information provided to the patients.

The PRAC considered the views of the experts and agreed that the benefits of these products in the indication at stake are limited and that this should be put in perspective of the potential safety risks, in particular in case of prolonged or repeated treatments.

It was also considered by the PRAC that the comments from the Member States in the referral procedure are in line with the experts' views. Estradiol-containing (0.01% w/w) medicinal products for topical use are marketed in few EU Member States only and no unmet medical need was reported. Of note, some national clinical practice guidelines (Dutch and draft German Guidelines) mention high-dose oestrogen-containing products but do not recommend their use.

Some women might need a re-treatment after the use of estradiol-containing (0.01% w/w) medicinal products for topical use. In such situation, the patients in line with the product information should be treated with other treatment options from non-pharmacological alternatives (vaginal moisturisers and lubricants which are the generally accepted international standards as first-line recommendations for the treatment of mild and moderate manifestations of vaginal atrophy), or pharmacological alternatives (vaginally applied oestrogen therapy containing estradiol or estriol, locally administered as ovule/ pessary or vaginal ring). In addition, the lowest effective dose for the shortest duration should be used.

In particular, topical treatments containing a dose of estradiol that do not lead to systemic exposure above normal postmenopausal range should be considered, in particular in view of the uncertain benefits and risks of estradiol-containing (0.01% w/w) medicinal products for topical use compared to low-dose products for topical use, the latter being better-characterised in terms of efficacy and safety.

The PRAC discussed whether specific medical examination (e.g. transvaginal ultrasound) could support the repetition of treatment courses but such measures were considered neither proportionate, nor effective, nor feasible in clinical practice. Indeed, transvaginal ultrasound is not adequate for monitoring endometrial safety during HRT as it does not allow excluding endometrial hyperplasia/ cancer in women (premenopausal or postmenopausal) on estrogen therapy that is unopposed or given with cyclic (rather than continuous) progesterone. Thickness thresholds are not well established for such women; as a result, endometrial sampling is still the gold standard to exclude endometrial hyperplasia and/or carcinoma.

The PRAC also discussed whether an interval between two treatment cycles could be introduced (e.g. one year) but as there are no data from clinical studies on the use of these products for longer than 4 weeks, neither data on repeated treatment courses, it is not possible to establish any scientific recommendation on a time-period for repeating the treatment courses. In the absence of evidence, no suitable repetition of treatment courses can be defined neither from the point of view of safety nor from efficacy.

Furthermore, such measures would not replace the missing safety data, and they cannot be accepted, in view of the seriousness of the undesirable effects associated with systemic exposure to estradiol (e.g. thromboembolism events, breast and endometrial cancers).

The PRAC finally noted that the measure of restriction to a treatment of only 4 weeks was in force since 2014 before the annulment of the relevant Commission Implementing Decision and did not raise any concern on its feasibility or effectiveness in clinical practice.

4.2.3. Conclusion on the benefit-risk balance following the re-examination procedure

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 submitted by Dr. August Wolff GmbH & Co. KG Arzneimittel (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 can not 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.

5. Risk management

5.1. Risk minimisation measures

5.1.1. Amendments to the product information

The PRAC considered that routine risk minimisation measures in the form of updates to the product information are necessary in order to minimise the risks associated with the use of estradiol 0.01w/w containing medicinal products.

The PRAC recommended the product information to be updated in accordance with the Core SmPC for HRT *elements for estrogen products for vaginal application of which the systemic exposure to the estrogen is higher than the normal postmenopausal range*.

In particular, the following amendments should be included.

As indication, in section 4.1 "Therapeutic indications" it is recommended to include the word "symptoms" of vaginal atrophy, and also indicate the fact that data for women older than 65 years is limited. The final indication should be:

> *"Treatment of symptoms of vaginal atrophy due to oestrogen deficiency in postmenopausal women.*
>
> *The experience treating women older than 65 years is limited."*

The section 4.2 "Posology and route of administration" was clarified and all currently available information is reflected. The safety information that for initiation and continuation of treatment of

postmenopausal symptoms, the lowest effective dose for the shortest duration should be used, is included.

Details on the method of administration process as well as on the initial and maintenance doses should be included.

No concomitant use of progesterone is necessary as the products should be used only for 4 weeks.

Additional information following the QRD template as these products should not be used in the paediatric population is also included in this section.

Further warnings and precautions of use relating to the known risks associated with the use of HRT were also included and other important information harmonised.

Warnings on the following excipients benzyl alcohol, cetyl stearyl alcohol and propylene glycol have been added to section 4.4.

In addition, the strength of the product should be mentioned as micrograms/g in the product information (SmPC, labelling and package leaflet) as per relevant guidelines[30].

The Package Leaflet was amended accordingly.

Finally, the Labelling has been updated to contain a warning message in the inner (immediate) and outer packaging stating that the duration of use is for only 4 weeks.

5.1.2. Pack size

The PRAC consider the package size of the products. It was agreed that the package size of 25 g is the adequate size for the 4-week treatment cycle. Package sizes above 25 g could lead to use of the product above 4 weeks and would therefore not be approvable.

5.1.3. Direct Healthcare Professional Communication and Communication plan

The PRAC considered that a Direct Healthcare Professional Communication (DHPC) was needed to raise awareness of the high strength of these medicinal products and their restricted duration of use. The specialists targeted are gynaecologists, general practitioners and any other relevant medical specialisations according to national healthcare systems. The communication is to be sent in accordance with the agreed communication plan. The DHPC agreed by the PRAC is provided together with the communication plan.

6. Grounds for 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

[30] https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/compilation-quality-review-documents-decisions-stylistic-matters-product-information_en.pdf

considered the grounds submitted by one MAH (Dr. August Wolff GmbH & Co. KG Arzneimittel) 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 Arzneimittel 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 above.

The Committee, as a consequence, recommends the variation to the terms of the marketing authorisations for estradiol-containing (0.01% w/w) medicinal products for topical use (pharmaceutical forms of cream and emulsion.