25 April 2014
EMA/281995/2014
Committee for Medicinal Products for Human Use

Assessment report for high concentration estradiol containing medicinal products for topical use

Referral under Article 31 of Directive 2001/83/EC

INN: estradiol

Procedure number: EMEA/H/A-31/1336

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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1. Background information on the procedure

1.1. Referral of the matter to the CHMP

On 24 May 2012, Germany triggered a referral under Article 31 of Directive 2001/83/EC. The CHMP was requested to give its opinion on whether the marketing authorisations for medicinal products containing estradiol for topical use should be maintained, varied, suspended or withdrawn.

The procedure described in Article 32 of Directive 2001/83/EC, was applicable.

2. Scientific discussion

2.1. Introduction

In May 2012, Germany (BfArM) requested the evaluation of the overall benefit-risk balance of high concentration estradiol (E2) containing medicinal products indicated for topical use for the treatment of vaginal atrophy (intravaginally and on the skin of vulva and vagina).

Germany was concerned that products containing estradiol which are indicated only for local use, exhibit high blood concentration upon application, which is seen only with products authorised for systemic use.

At start of procedure, data from different medicinal products and formulations authorised for local vaginal use (vaginal tablets, gel, ring etc.) were considered. However at the early stages of the assessment the CHMP concluded that some of these products should no longer be part of this assessment as their concentration and dose were considered low and therefore did not fulfill the scope of this procedure. The products which were identified according to the scope of the referral notification were two groups, represented by 0.01% w/w estradiol (Linoladiol N and other names, hereafter referred to as Linoladiol N) and 0.005% w/w estradiol and 0.4%w/w prednisolone (Linoladiol HN, and other names, hereafter referred to as Linoladiol HN).

Linoladiol N and Linoladiol HN are approved by national procedures in different member states.

The indications in the summary of product characteristics (SmPC) for these products may differ slightly depending on the national authorisations. For Linoladiol N the therapeutic indication approved is *"treatment of atrophic vulvovaginal disorders attributable to oestrogen deficiency"*. Linoladiol HN is indicated *"for the initial short-term external treatment of acute, mild, inflamed, burning and itching skin diseases of the external female genital area, for which weak-acting corticosteroids and low-dose estradiol are indicated".* In addition the therapeutic indication approved in some member states includes the skin disorder *lichen sclerosus genitalis*.

2.2. Linoladiol N

Linoladiol N (cream) contains 0.01 % w/w estradiol i.e. 100 g cream contain 103.3 microgram (mcg) estradiol hemihydrate (equivalent to 100 mcg estradiol).

It is a prescription-only medicine and is to be used only under regular medical control.

The route of administration is intravaginal use and cutaneous use in the external genital area. The recommended dose for diseases of the vaginal entrance and external genital area is 1 cm of cream onto the skin once or twice daily; and the recommended dose for vaginal diseases itself is 2 g cream

(200 mcg estradiol) administered intravaginally using an applicator every other day during the first week of treatment and twice weekly thereafter.

2.2.1. Clinical pharmacokinetics for Linoladiol N

The CHMP assessed all available data submitted by the MAHs. The main pharmacokinetic studies submitted are presented below.

Intravaginal application

Study SCO 5109

An explorative, single-centre, one period study on estradiol was performed to determine the bioavailability of estradiol from Linoladiol N in 16 healthy postmenopausal women aged between 45 and 70 years of age. The primary objective of the study was to estimate the extent of estradiol exposure after application of the test formulation Linoladiol N.

Inclusion criteria were *inter alia* plasma estradiol levels of <10 pg/ml and follicle stimulating hormone (FSH) levels of > 40 IU/l to ensure a definite postmenopausal condition. The women received a single dose of 2.0 g of the Linoladiol N cream, corresponding to 200 mcg estradiol. Blood sampling was taken at defined time intervals between 0 – 36 hours after administration of Linoladiol N.

Primary variables were $AUC_{\delta 0\text{-}36}$ and $C_{\delta max}$ of estradiol, i.e. the extent of exposure was estimated as area under the baseline adjusted estradiol concentration curve and the baseline-adjusted maximal plasma concentration of estradiol.

The *mean* value of $AUC_{0\text{-}36}$ (1285.2 pg/ml·h) and C_{max} (103.5 pg/ml) indicate systemic exposure to estradiol from the intravaginal cream. Estradiol serum concentrations were determined by radioimmuno-assay (RIA), with the following main results: baseline-adjusted $AUC_{\delta 0\text{-}36}$ 900.8 pg/ml h, baseline-adjusted $C_{\delta max}$ 92.2 pg/ml. The adjusted mean $C_{\delta max}$ (92.2 pg/ml) amounted to 89% of the total C_{max}.

The peak concentration of estradiol was reached six hours after application (median). Thirty six hours after application, the estradiol concentrations had returned to the pre-dose baseline concentration in the majority of subjects. The mean baseline estradiol serum concentration was 11.3 pg/ml. The mean estradiol serum concentration at 36 h which is the last time point blood samples were drawn was 10.7pg/ml. The terminal half-life (geometric mean 5.05 h) was subject to high inter-subject variability.

Study SCO 5174

In a randomised, double-blind, placebo-controlled parallel group post-authorisation study investigating the efficacy and safety of Linoladiol N in the treatment of 48 postmenopausal women with vaginal atrophy, the primary test parameter was the vaginal maturation index (VMI). Secondary test parameters included symptoms of vaginal atrophy and vaginal pH.

With regards to the VMI, Linoladiol N was statistically significantly superior to placebo (mean VMI Linoladiol N group: at baseline 24.47%, on day 31, 64.23%; placebo group: baseline 32.01%, day 31, 37.17%). In terms of secondary endpoints, a decrease in vaginal pH was observed in the Linoladiol N group (mean vaginal pH at baseline 6.0, on day 31, 4.2) compared to placebo (mean vaginal pH at baseline 6.2, on day 31, 5.9). Symptoms of vaginal atrophy such as pruritus and dyspareunia decreased in both groups. No significant differences between Linoladiol N and placebo were observed in this regard.

In this study SCO 5174, mean estradiol serum concentrations at baseline and at day 31 (i.e. about 36h after administration of study medication on day 29) were 6.4 pg/ml and 15.1 pg/ml, respectively, in the Linoladiol N group and 4.4 pg/ml and 6.2 pg/ml, respectively, in the placebo group.

Dermal application

More recently, the MAH has performed two new post-authorisation studies with *dermally* applied Linoladiol N in which inter alia pharmacokinetic data with regard to serum estradiol were collected.

One (1) cm of Linoladiol N cream corresponds approximately to 0.2–0.25 g cream (200–250 mg cream, containing 20–25 mcg estradiol).

With an assumed vulvar surface area of 200 cm^2 (Bubendorf *et al.,* 2011; Long and Finlay, 1991; Niemeyer *et al.,* 2005) and an applied amount of 1 mg or 2 mg of cream per cm^2 skin area one would therefore calculate an amount of 200 mg or 400 mg cream. Thus, with the recommendation to use 1 cm Linoladiol N cream (corresponding to 200 mg to 250 mg cream) to the vulva the same amount of cream is applied.

Study Eudra CT-No. 2010-020364-37

The study was performed as a first step in a clinical development program for a locally acting estradiol formulation in the treatment of dermatoporosis (chronic cutaneous insufficiency / fragility syndrome).

In this first study, the systemic bioavailability and the kinetics of estradiol from dermal application of Linoladiol N were investigated. The objective of the study was to demonstrate that the application of an adequate dose of a locally acting cream containing 0.01 % w/w estradiol (Linoladiol N) does not increase the estradiol (E2) plasma concentration to an amount exceeding 5 pg/ml, which is considered to be within the range of the natural occurring variability in postmenopausal subjects.

One single treatment was investigated. Twenty-four postmenopausal women received a single dose of 2 mg cream/cm^2 skin, administered topically on 4250 cm^2 skin surface, on defined skin areas of the back, stomach and both thighs. The total amount of applied cream was 8.50 g, corresponding to 850 mcg estradiol, a high dose.

Blood sampling was performed 24 h and 0 h before application of the cream, and several intervals until 48 hours after application. The plasma concentrations of estradiol (E2) were measured by liquid chromatography-mass spectrometry (LC-MS/MS), with a calibration range of 3 to 200 pg/ml. The accuracy ranged from 91.9% at 3 pg/ml to 106.9% at 6 pg/ml.

There was a high intra-individual variability of E2 concentrations at baseline and during the blood sampling period of 48 hours. The mean pre-dose baseline of endogenous E2 was 3.0 pg/ml (range 0 to 8.53 pg/ml). The baseline adjusted E2 mean concentrations returned to a minimum of 0.637 pg/ml 8 h after application, re-increased to 1.99 pg/ml 24 h after application and decreased to 1.12 pg/ml 48 h after application.

Within the measurement interval of 48 h following the application of the cream, the mean E2 concentrations after a single-dose application maximally increased by 3.49 pg/ml – in terms of $\delta C_{max0\text{-}48\ h}$ – to a total maximal concentration C_{max} of 6.49 pg/ml. The individual maximal increases $\delta C_{max0\text{-}48h}$ ranged from 0 to 12.39 pg/ml. Following local application of 8.50 g Linoladiol N (corresponding to 850 mcg E2), an increase in E2 plasma levels was observed for 22 out of 24 subjects. The individual maximal increases $\delta C_{max0\text{-}48h}$ remained below a limit of < 5 pg/ml in 20 of 24 subjects.

Altogether, the upper 95% confidence bounds for the maximal increases $\delta C_{max0-48h}$ (3.49 pg/ml [2.56 – 4.41 pg/ml]) and $\delta C_{max0-24h}$ (3.33. pg/ml [2.43 – 4.24 pg/ml]) did not exceed a threshold of 5 pg/ml and thus did not exceed the critical threshold of + 5pg/ml stipulated in the study protocol.

Study Eudra CT-No. 2011-002464-24

In this randomised, double-blind, placebo-controlled phase IIa clinical study, Linoladiol N (or placebo) was applied once daily in an intra-individual comparison to the skin of the forearms of 44 women over a period of 8 weeks. Only postmenopausal women with a baseline serum estradiol < 30 pg/ml were included. For each application an amount of 1 mg cream/cm^2 skin was used. Estradiol (E2), follicle-stimulating hormone (FSH) and luteinizing hormone (LH) serum concentrations were assessed at baseline, after 12, 14 and 16 days of treatment as well as after 8 weeks of treatment.

The mean estradiol level at baseline was 14.18 pg/ml; mean estradiol levels did not change significantly over the treatment period of 8 weeks. At day 56 (i.e. after 8 weeks), the mean estradiol level was 11.04 pg/ml. In 4 patients, serum estradiol exceeded 30 pg/ml (two patients presented at day 13 with 31.5 pg/ml and 31.7 pg/ml; two patients presented at day 15 with 30.3 pg/ml and 31.7 pg/ml). Although the treatment was not changed, serum E2 levels were decreased at the following laboratory evaluation in these patients and were in the following measurements all below 30 pg/ml. There were no significant changes in FSH and LH levels.

Once daily topical application of Linoladiol N in an amount of 1mg cream per cm^2 to the skin of one forearm over a period of 8 weeks did not lead to significant changes in serum levels of estradiol, FSH or LH.

Based on the PK data provided, the MAH was asked by the CHMP to justify the dosing regimen of 1 cm Linoladiol N cream administered once or twice daily on the skin of the external vaginal area.

The MAH responded that in the application of ointments or creams to the skin it is usual to assume (e.g. in clinical studies in dermatology) an amount of 1 mg or 2 mg cream per cm^2 skin area. As Linoladiol N exhibits a very good spreadability, an amount of 1 mg cream per cm^2 skin is sufficient to treat the vulvar region. With regard to the above mentioned PK data from the study with dermally applied Linoladiol N (Eudra CT-No. 2010-020364-37) and taking into consideration the fact that the applied dose of Linoladiol N cream in this PK study exceeds the dose recommended for vulvar application by a factor of 34, (worst case scenario), the MAH extrapolated that twice daily application of Linoladiol N to the vulva does not impose a systemic risk.

The CHMP considered that in the two described studies, Linoladiol N cream was administered on the skin of the back, stomach and thighs (*Eudra CT-No. 2010-020364-37*) or forearms (*Eudra CT-No. 2011-002464-24*). It is highly questionable whether absorption of estradiol from the skin of these body areas is comparable to absorption from the vulva. Although the principal structure of the epidermis is the same there may be differences regarding the thickness of the epidermis and its single strata. In addition, other factors like the application on inflamed skin, application in the area of vulva and associated occlusive effects may also impact on the absorption. It is also not unlikely that some of the Linoladiol N cream is administered unintentionally to the vagina. All these factors would be expected to increase absorption of estradiol. In addition, the statement of the MAH that the applied dose of Linoladiol N cream in the above mentioned PK study exceeds the dose recommended for vulvar application by a factor of 34 is not accepted. Thus, with respect to the administration site as well as with respect to the dose of cream per cm^2 skin, the submitted studies are not in accordance with the dose recommendations for Linoladiol N. The available PK data on administration of Linoladiol N on the

skin of the back, abdomen, thigh or forearm should therefore not be extrapolated to the dosing regimen of Linoladiol N for administration on the skin of the vulva in the SmPC.

Cutaneous use in the external genital area

No studies were performed on the cutaneous use of Linoladiol N in the external genital area.

Comparison of different topical estradiol containing products

The CHMP noted that the maintenance dose recommended for Linoladiol N (200 mcg estradiol twice weekly, i.e. 400 mcg estradiol/week) is about 8 times higher than the maintenance dose of estradiol 25 mcg vaginal tablets (25 mcg estradiol twice weekly, i.e. 50 mcg/week) and estradiol vaginal ring (release rate 7.5 mcg estradiol per 24 h, i.e. 52.5 mcg/week) and 20 times higher than the maintenance dose of estradiol 10 mcg vaginal tablets (10 mcg estradiol twice weekly, i.e. 20 mcg/week).

The CHMP agreed with the MAH that not only dose, but also absorption and systemic concentrations of topically administered estradiol are of interest.

An analysis of PK data of estradiol after vaginal application across several published studies has been performed during the assessment of this referral and the data are shown in the table below.

Table 1. Comparison of PK data for estradiol containing medicinal products for topical use (intravaginally)

	Vagifem 10 mcg	**Vagifem 25 mcg**	**Estring 2 mg**	**Linoladiol N**
Pharmaceutical form	Vaginal tablets	Vaginal tablets	Silicone ring	Cream (200mcg E2/ 2g)
Single dose estradiol	10 mcg	25 mcg	First appl. for 12 weeks	200 mcg
C_{max} [pmol/L]	152 (n=47)	206 (n=43)	232 (n=14)	393 (n=29)
$C_{average}$ [pmol/L]	54 (n=47)	86 (n=43)	27 (n=14)	178 (n=29)
C_{max} [pg/ml]	41.5	56.0	63.2	107
$C_{average}$ [pg/ml]	14.8	23.5	7.4	48.6
Multiple doses	10 mcg biweekly	25 mcg biweekly	for 12 weeks each	200 mcg biweekly
C_{max} [pmol/L]	81 (n=23)	180 (n=19)	163 (n=14)	-
$C_{average}$ [pmol/L]	32.5 (n=23)	64 (n=25)	-	85 [1] (n=13)
C_{max} [pg/ml]	22.0	49.0	44.4	-
$C_{average}$ [pg/ml] [2]	8.9	17.4	-	23.1

Note: Presenting arithmetic means. Since AUCs were determined in the different sources over varying intervals, only $C_{average}$ is summarised.
All results without baseline correction. Mean baselines reported for the studies summarized here varied from 11.5 to 127 pmol/L, weighted mean 23.9 pmol/L or 6.5 pg/ml. Studies however used different bioanalytical methods and results lower than the analytical quantification limit were not handled always in the same way, such that inter-study comparisons have to be interpreted with caution.

1. Geometric mean, derived by extrapolation
2. The molecular weight of estradiol is 272.38 g/mol. Therefore, 1 pmol/L corresponds to 0.272 pg/mol, vice versa, 1 pg/ml corresponds to 3.67 pmol/L

With the exception of estradiol vaginal ring, all other estradiol-containing preparations are administered intravaginally bi-weekly during maintenance therapy, in consequence leading to two estradiol plasma peaks per week.

After a single dose of estradiol vaginal tablets 10 mcg, C_{max} without baseline correction is less than half and $C_{average}$ in the 24 h interval after dosing without baseline correction is about one third of the respective values of Linoladiol N (see table above).

Regarding estradiol vaginal ring, estradiol concentration without baseline correction remained within the postmenopausal range, except for a peak occurring after insertion/change of the ring which appears to be still lower than C_{max} after administration of Linoladiol N. Due to the fact that an Estring vaginal insert is replaced by a new one every three months, these peaks are not considered as clinically relevant.

Of the three comparators discussed, estradiol vaginal tablets 25 mcg is associated with the highest systemic exposure to estradiol and is discussed in more detail. After a single dose of estradiol vaginal tablets 25 mcg, C_{max} without baseline correction was 206 pmol/l, while $C_{average}$ without baseline correction during the first 24 h was 86 pmol/l based on the studies by Notelovitz (2002) and Nilsson and Heimer (1992). In comparison, after a single dose of Linoladiol N, C_{max} without baseline correction was 393 pmol/l, $C_{average}$ without baseline correction during the first 24 h was 178 pmol/l based on the studies by Lauritzen (1992), Göres (1995) and Mazur (2003).

Taking into account baseline corrected values, C_{max} and $C_{average}$ in the 24 h interval after drug administration were 175 pmol/l and 55 pmol/l, respectively, regarding estradiol vaginal tablets 25 mcg, and 331 pmol/l and 120 pmol/l, respectively, regarding Linoladiol N.

Conclusions on pharmacokinetic data on Linoladiol N

Intravaginal administration

In study SCO 5109, pharmacokinetics of estradiol after a single dose of 2 g Linoladiol N cream corresponding to 200 mcg estradiol administered intravaginally were studied in 16 postmenopausal women. Estradiol serum concentrations were determined by radioimmuno-assay (RIA), with the following main results: baseline-adjusted $AUC_{\delta 0\text{-}36}$ 900.8 pg/ml h, baseline-adjusted $C_{\delta max}$ 92.2 pg/ml. The mean baseline estradiol serum concentration was 11.3 pg/ml. The mean estradiol serum concentration at 36 h which is the last time point blood samples were drawn was 10.7 pg/ml.

In the randomised double-blind placebo-controlled study SCO 5174, mean estradiol serum concentrations at baseline and at day 31 (i.e. about 36 h after administration of study medication on day 29) were 6.4 pg/ml and 15.1 pg/ml, respectively, in the Linoladiol N group and 4.4 pg/ml and 6.2 pg/ml, respectively, in the placebo group.
The CHMP noted that the pharmacokinetic data demonstrate that estradiol is absorbed after vaginal application of Linoladiol N cream. Systemic effects can be expected as the estradiol levels are increased above postmenopausal levels which range from 10-20 pg/ml.[1]

Administration on the skin of the genital area

No pharmacokinetic data regarding administration of 1 cm Linoladiol N cream once or twice daily on the skin of the external genital area were submitted. As detailed above, the results of the studies investigating absorption of estradiol after administration of Linoladiol N on the skin of the back, abdomen, thigh and forearm cannot be extrapolated to application of Linoladiol N on the skin of the vulva.

1 Clinical Gynaecologic Endocrinology and Infertility, 8e, Marc A Fritzand, Leon Speroff (Chapter 17: menopause and the peri-menopausal transition)

Systemic levels of estradiol are of interest with respect to safety. Based on study SCO 5109, it is concluded that twice weekly estradiol serum levels similar to those reached with systemic Hormonal replacement therapy (HRT) are observed. In addition, in Study 5174 was observed that estradiol serum concentrations had not returned to baseline levels about 36 h after administration of Linoladiol N.

Despite the limitations of historical comparisons with other locally applied medicinal products, it can be concluded that exposure to estradiol after administration of Linoladiol N is considerably higher than after administration of other lower dosed estradiol products for topical intravaginal therapy. The fact that the weekly exposure is higher and the long-term exposure in daily clinical practice are important factors that need to be taken into account.

In summary, the pharmacokinetics of the dosing regimen of Linoladiol N administered on the skin of the vulva were not investigated. The systemic concentrations of estradiol observed after intravaginal administration of 2 g Linoladiol N cream twice weekly are considerably higher compared to other estradiol products for topical vaginal treatment and raise safety concerns.

2.2.2. Clinical efficacy of Linoladiol N

Study SCO 5174

In the clinical study SCO 5174 (2004), in the first week, 2 g of cream (200 mcg estradiol) were applied vaginally every other day (i.e. at intervals of 48 hours), and thereafter twice a week.

Pharmacokinetic data showed mean estradiol concentrations of 15.1 pg/ml on day 31, i.e. 36 h after the last application of study medication, after 4 weeks of 'fractionated' use of Linoladiol N.

The study has been discussed above in more detail.

Studies on dose finding

No studies on dose finding were performed.
Taking into account that other estradiol products approved for topical treatment of vulvovaginal atrophy are administered in considerably lower dosages, lower doses of Linoladiol N might probably be sufficient for topical treatment of vulvovaginal atrophy. However, doses lower than those recommended for Linoladiol N were not investigated.

Conclusion on efficacy of Linoladiol N

Clinical studies with regard to dose finding were not performed. In one randomised double-blind placebo-controlled study, intravaginal treatment with Linoladiol N was superior to placebo with regard to objective parameters such as VMI, but not with regard to subjective symptoms of vulvovaginal atrophy such as vaginal pruritus or dyspareunia. Alleviation of these symptoms is considered clinically relevant. In view of the high dose of estradiol administered with Linoladiol N, this medicinal product is effective in the treatment of symptoms of vaginal atrophy. Furthermore the fact that the weekly exposure of estradiol is higher for Linoladiol N than other estradiol-containing products for vaginal use, and the long-term exposure in daily clinical practice are important factors that should be taken into account within the benefit-risk analyses. The treatment regimen should be amended according to the scientific data. Treatment should be restricted to only vaginal application (and not on the skin of vulva) and the treatment duration should be limited to four weeks according to the clinical studies performed.

2.3. Linoladiol HN

Linoladiol HN (cream) contains 0.005%w/w estradiol and 0.4%w/w prednisolone i.e. 51.6 mcg estradiol hemihydrate (equivalent to 50 mcg estradiol) and 0.430 g prednisolone-1.5 H_2O (equivalent to 0.400 g prednisolone) per 100 g cream for cutaneous use.

The route of administration is cutaneous. Unless otherwise prescribed, Linoladiol-HN (approximately 1 cm of cream) is thinly applied once to twice daily onto diseased skin areas. In most cases, Linoladiol HN is used for 2-3 weeks. Application beyond 4 weeks is needed in isolated cases only. The healthcare professional will decide on the duration of treatment, and whether further treatment is needed with another medicinal product with no corticosteroid or a cream with no active substances.

2.3.1. Clinical Pharmacokinetics for Linoladiol HN

No pharmacokinetic data have been submitted for the Linoladiol HN medicinal product. The MAH referred to the Linoladiol N submitted studies. It was noted that Linoladiol N does not contain prednisolone and the concentration of estradiol is higher compared to Linoladiol HN.

2.3.2. Clinical efficacy Linoladiol HN

Clinical studies investigating the efficacy of Linoladiol HN in the authorised indications are not available. Concerning the second active substance, prednisolone, the MAH stated that the use of corticosteroids to the vulva belongs to standard therapy of skin diseases in this skin area and did not give rise to concerns with respect to women's health. Usually, as e.g. for the treatment of *lichen sclerosus* on the vulva, even stronger corticosteroids than prednisolone, i.e. clobetasol propionate are used[2] .

The MAH argued that with regard to the combination of estradiol with corticosteroid, vulvar irritation and discomfort is often experienced by postmenopausal patients with atrophic vulvovaginitis. While an oestrogen addresses oestrogen deficiency, a corticosteroid is added for the treatment of symptoms of acutely inflamed skin, such as burning and itching. The combination of an oestrogen and a corticosteroid for topical treatment of atrophic vulvovaginitis is not discussed in the literature and no publications regarding fixed combinations of an oestrogen and a corticosteroid were provided.

In summary, Linoladiol HN administered on the skin of the vulva is used in the treatment of acute, mild, inflamed, burning and itching skin diseases of the external female genital area, for which weak-acting corticosteroids and low dose estradiol are indicated. The product is also indicated in the treatment of atrophic vulva disorders attributable to oestrogen deficiency or *lichen sclerosus* in women genitals.

Studies on dose finding

No dose-finding studies were performed with Linoladiol HN.

[2] http://www.asccp.org/PracticeManagement/Vulva/BenignandInflammatoryConditionsoftheVulva/LichenSclerosus/tabid/7438/Default.aspx

Conclusion on efficacy on Linoladiol HN

Efficacy of Linoladiol HN was not studied in any clinical trial. In addition, there are no clinical studies or other literature references referring to the treatment of atrophic vulvovaginitis with Linoladiol HN or other fixed combinations of an oestrogen and a corticosteroid. Moreover, according to current textbooks, estradiol is not a treatment option for *lichen sclerosus* of the vulva (Weller, 2008; Jain, 2012). Therefore, Linoladiol HN should not be used to treat *lichen sclerosus genitalis* in women.

The absorption of estradiol and prednisolone might be different after administration of an estradiol-containing product on the (inflamed) vulva, therefore data available from Linoladiol N cannot be directly extrapolated.

Although the product is indicated for treatment not longer than 4 weeks, in clinical practice there might be a risk of use more than 4 weeks resulting in extended exposure to estradiol and a corticosteroid, and its related risks. The treatment should be restricted to a treatment duration limited to four weeks and in postmenopausal patients only.

2.4. Clinical safety

All safety information on Linoladiol N and Linoladiol HN from clinical studies, post-marketing data and published literature have been assessed during procedure. Relevant information is presented hereinafter.

2.4.1. Linoladiol N

Endometrial safety

In the randomised, double-blind, placebo-controlled clinical study SCO 5174, forty-eight postmenopausal women self-administered either 2 g of the study drug (= 200 mcg estradiol) or a placebo cream for four weeks. In the first week, the creams were used three times at 48-hour intervals. In weeks 2 to 4, the application intervals were 3 and 4 days, respectively (twice weekly). The endometrial thickness was measured sonographically before starting treatment and after termination of the treatment. The mean endometrial thickness showed only non-significant changes, from a baseline value of 2.7 to 3.4 mm in the Linoladiol N group and from a baseline value of 3.0 mm to 3.2 mm in the placebo group after 31 days of therapy with the applied treatment scheme.

The MAH argued that Linoladiol N for the treatment of vulvovaginal atrophy is not comparable to oestrogens for systemic hormone replacement therapy (HRT), either for oral or transdermal application (daily application, daily elevated estradiol serum levels) because of its lower frequency of application (only twice weekly) and the resulting lower mean estradiol level in blood (as described for this study SCO 5174 in the pharmacokinetic section). Endometrium biopsies for detecting the endometrial safety of Linoladiol N were therefore not considered necessary by the MAH. The CHMP argued that as vaginal atrophy is a long-term condition which warrantees long-term treatment, the cumulative effect of systemic absorption of estradiol cannot be excluded, for women subjected to these high concentrations twice weekly.

Although no endometrium hyperplasia is anticipated using the recommended treatment regimen (twice weekly administration) of Linoladiol N, the MAH recommended examinations such as ultrasound of the endometrium and a progestin challenge test in the current SmPC. The CHMP is of the opinion that data on endometrial thickness after treatment duration of four weeks are available from study SCO 5174. Nevertheless, neither is endometrial thickness acceptable as the primary endpoint regarding

endometrial safety nor is the treatment duration of four weeks sufficient for the detection of endometrial hyperplasia (see EMA Guideline on HRT)[3].

With regard to post-marketing data, it is noted that no observational studies regarding endometrial safety of Linoladiol N are available. Based on spontaneous reporting, no risk signal was detected. However, in particular with regard to older medicinal products, substantial under-reporting of adverse effects has to be assumed.

The MAH was requested to justify that Linoladiol does not need to be combined with a progestagen for endometrial protection, taking into account systemic exposure to estradiol during treatment and the requirements according to the Guideline on clinical investigation of medicinal products for hormone replacement therapy of oestrogen deficiency symptoms in postmenopausal women (EMEA/CHMP/021/97, Rev. 1).

The MAH response was that the guideline in reference, deals with medicinal products for hormone replacement therapy, i.e. for oestrogen deficiency symptoms in postmenopausal women such as hot flushes and it would not be applicable to medicinal products containing oestrogen for vaginal use. This argument was not accepted by the CHMP, as the guideline is applicable to all medicinal products containing an oestrogen and indicated to relieve HRT symptoms, as is the case of Linoladiol N. However, the CHMP noted that if the treatment is restricted in its duration of use and a recommendation is given to physicians for careful monitoring of the patients for any signs of endometrial proliferation, then the addition of a progestogen to the treatment may not be specifically included.

In summary, the CHMP concluded that the endometrial safety of Linoladiol N was insufficiently studied. Therefore, it remains unknown whether addition of a progestagen is required to protect the endometrium. Although this is not acceptable for an oestrogen product for topical therapy of vulvovaginal atrophy, if limitation to the duration of treatment can be ensured as per the duration studied in SCO 5174 then the concerns on endometrial safety may be limited together with the close monitoring by the physicians for endometrial proliferation; (see also the discussion on long-term use below).

Long-term use

The CHMP noted that based on the indication “atrophic vulvovaginal disorders attributable to oestrogen deficiency” long term use of the Linoladiol N can be expected. The estradiol-related risk will increase with prolonged use of the product.

The MAH presented in their responses that the benefit of Linoladiol N has been substantiated by the results of the clinical study in postmenopausal women which showed an improvement of all objective parameters of vaginal atrophy (SCO 5174). Moreover, the MAH argued that it is known from literature that estradiol absorption from vaginal application decreases over time (Notelovitz *et al.,* 2002; Nilsson *et al.,* 1992; Calstrom *et al.,* 1982). It is assumed that this is due to the maturation state of the vaginal epithelium, i.e. absorption is highly reduced when the epithelium is mature (Deutch *et al.,* 1981), which is in line with the statement of Henrikson and colleagues (1994) that thin, atrophic vaginal mucosa absorbs estradiol more effectively than does thickened, mature mucosa. With regard to the possible risks concerning vulvar use of Linoladiol N, PK data from the above mentioned study Eudra CT-No. 2011-002464-24 with a dermal application of Linoladiol N over a period of 8 weeks did not show any relevant elevation of serum estradiol levels. The MAH argued that there is no substantial

[3] Guideline on clinical investigation of medicinal products for hormone replacement therapy of oestrogen deficiency symptoms in postmenopausal women, EMEA/CHMP/021/97 Rev. 1, October 2005

evidence for a risk by vulvovaginal long-term use of Linoladiol N if used according to the posology described in the SmPC.

For intravaginal administration, the CHMP noted that systemic exposure to estradiol after long-term administration of Linoladiol N was not investigated. Thus, it is unknown if or to what extent systemic exposure might be decreasing with increasing treatment duration, as hypothesised by the MAH. After twice weekly application of Linoladiol N cream, the estradiol serum concentrations are as high as with medium dosed systemic HRT (Estradiol transdermal patches 50 mcg/day, estradiol 1mg p.o.). Therefore Linoladiol N has systemic effects, which means that the well-known risks of systemic HRT must be taken into account for the benefit risk balance of Linoladiol N. In postmenopausal women, vaginal atrophy is expected to recur when administration of an oestrogen is discontinued; repeated administration of oestrogen must therefore be expected.

Vulvar administration of Linoladiol N

With regards to vulvar administration of Linoladiol N, there are no clinical studies investigating pharmacokinetic properties, the dosing regimen, efficacy and safety of Linoladiol N administered on the skin of the vulva, and justification based on public literature has not been provided. According to current textbooks, estradiol is not a treatment option for vulvar disorder such as *lichen sclerosus* or *vulvar pruritus*.

Pharmacovigilance data

The periodic safety update reports (PSURs) covering the period from 17 March 2003 to 17 January 2011 for Linoladiol N included 11 case reports (10 from literature, 1 from the MAH) that reported extensive endometriosis (1), deep venous thrombosis (1), oestrogen-dependent breast cancer (1), endometrial adenocarcinoma (1), pulmonary embolism (2), transplant failure due to potential interaction with tacrolimus (1), myocardial infarction (1), endometrial sarcoma (1), hypertensive crisis (1), skin hyperpigmentation (1), and shock (1). Most of the cases reported in literature seem to refer to other oestrogen products such as transdermal patches or transdermal gel. Thus, these single cases do not confirm a safety issue for Linoladiol N.

In addition to endometrial safety concerns, known risks for systemic oestrogen-containing products for HRT are breast cancer, ovarian cancer, venous thromboembolism, ischaemic stroke.

Conclusion on safety Linoladiol N

The CHMP reviewed all available clinical and post-marketing data for the products containing 0.01% w/w estradiol (Linoladiol N, cream), and 0.005% w/w estradiol and 0.4%w/w prednisolone (Linoladiol N, cream). The CHMP recognised that the data is sparse. In addition no prospective evaluation of safety, in particular endometrial safety was available.

Regarding 0.01% w/w estradiol containing products pharmacokinetic data indicate a clinically relevant systemic exposure to estradiol which is clearly higher than with other intravaginally administered estradiol products, is not required for topical therapy, and raises concerns, in view of the well-known risks of systemic HRT.

In terms of pharmacovigilance, data and in the PSURs covering the period from 17 March 2003 to 17 January 2011 indicated that a total of eleven cases were reported. These included spontaneous reports and literature cases. Three of these cases reported endometrial events: extensive endometriosis (1), endometrial adenocarcinoma (1), endometrial sarcoma (1). Although there is a large post-marketing experience, no definite conclusions regarding safety, in particular endometrial

safety can be drawn based on post-marketing data, due to the low number of total reported cases for these products and possible under-reporting of adverse reactions, in particular for products already marketed for a considerable period of time, such as Linoladiol N. In addition known risks for systemic oestrogen-containing products for HRT are breast cancer, ovarian cancer, venous thromboembolism, ischaemic stroke.

On the basis of the available data the CHMP considered that the duration of treatment should be restricted to four weeks, and clear information should be reflected in the posology section. In addition, given the potential risks linked with all HRT treatments, information on which conditions need to be supervised and appropriate warnings on e.g. endometrial hyperplasia and carcinoma, breast and ovarian cancer, need to be reflected in the appropriate sections of the product information.

2.4.2. Linoladiol HN

Linoladiol HN is a combination of prednisolone and estradiol, with prednisolone as the main component with regard to the intended therapeutic effect.

The CHMP requested to the MAH to submit all relevant safety data regarding Linoladiol HN administered on the skin of the vulva. The MAH responded that due to the content of the corticosteroid prednisolone (which may, as is well known, cause atrophic changes in the skin tissue with long-term use), use of Linoladiol HN is recommended only for short time therapy (up to four weeks).

During the assessment phase of this referral, the CHMP requested the MAH to justify whether there is the need of addition of a progestagen according to the guideline on HRT products, as this will provide endometrial protection. The MAH argued that this guideline for hormone replacement therapy of oestrogen deficiency symptoms in postmenopausal women (EMEA/CHMP/021/97, Rev. 1) is not applicable to Linoladiol HN because this medicinal product is not intended to be used as a hormone replacement therapeutic in oestrogen deficiency symptoms in postmenopausal women. The CHMP agreed that the addition of a progestogen should not be recommended if the treatment duration is limited to 4 weeks.

The indication for Linoladiol HN is *"For the initial short-term external treatment of acute, mild, inflamed, burning and itching skin diseases of the external female genital area, for which weak-acting corticosteroids and low-dose estradiol are indicated."* The CHMP recommended that the use only in postmenopausal women should be explicitly stated in the indication.

In terms of pharmacovigilance data the MAH submitted PSURs covering the period from 17 March 2003 to 17 January 2011. In the PSURs, several cases of hypersensitivity reactions/drug intolerance after administration of Linoladiol HN were reported. No serious adverse reactions after administration of Linoladil HN were reported.

The CHMP concluded that the endometrial safety of Linoladiol HN has not been sufficiently studied. Data on the absorption of estradiol after administration of Linoladiol HN on the skin of the vulva is also not available.

It is also noted that dermal application of corticosteroids often results in dermal and epidermal thinning especially in areas of high absorption such as skin folds, the face and the nappy area although according to few literature references topical prednisolone 0.4% w/w is considered as a corticosteroid of weak activity, leading to hardly recognizable thinning of the upper skin layer. The (inflamed) vulva and anus are also expected to be an area of high absorption. Due to epidermal thinning the absorption

of corticosteroids may increase and it cannot be excluded that the dermal absorption of oestrogens is also affected.

However, it is agreed that since approval of Linoladiol HN no new risk signals with respect to endometrial safety were detected, based on post-marketing data.

Conclusions on safety on Linoladiol HN

In view of the fact that no clinical studies investigating Linoladiol HN are available, the CHMP took into account post-marketing data on Linoladiol HN.

Linoladiol HN is approved in for *"initial short-term external treatment of acute, mild, inflamed, burning and itching skin diseases of the external female genital area, for which weak-acting corticosteroids and low-dose estradiol are indicated"* in several member states. The CHMP recommended adding a clear reference to the patient population (postmenopausal women).

In addition the therapeutic indication approved in some Member States includes the skin disorder *lichen sclerosus genitalis* i.e. *"For the treatment of atrophic vulva disorders attributable to oestrogen deficiency, lichen sclerosus in women genitals".* According to current clinical knowledge on the treatment of this condition, estradiol is not a treatment option for *lichen sclerosus* of the vulva.[4,5] The CHMP therefore recommended its deletion from the product information.

In addition, the CHMP considered that the duration of treatment should be restricted to four weeks due to the presence of corticosteroid in the formulation, and clear information should be reflected in the posology section. In addition, given the potential risks linked with all HRT treatments, information on which conditions need to be supervised and appropriate warnings on e.g. endometrial hyperplasia and carcinoma, breast and ovarian cancer, need to be reflected in the appropriate sections of the product information.

2.5. Overall conclusion and benefit-risk assessment

In May 2012, Germany (BfArM) requested the evaluation of the overall benefit risk balance of high concentration estradiol (E2) containing medicinal products indicated for topical use for the treatment of vaginal atrophy (intravaginally and on the skin of vulva and vagina). Germany was concerned that products containing estradiol which are indicated only for local use, exhibit high blood concentration upon application, which is seen only with products authorised for systemic use.

Two group of products represented by Linoladiol N (cream, 0.01% w/w estradiol), and Linoladiol HN (cream, 0.005% w/w estradiol and 0.4%w/w prednisolone) were assessed in this procedure. Linoladiol N and Linoladiol HN are approved via national procedures in different member states.

2.5.1. Linoladiol N

The CHMP took into account all available data on pharmacokinetics, dose-finding, efficacy and safety, including endometrial safety, of products for intravaginal administration and/or administration on the skin of the vulva containing estradiol and also the well-known risks of systemic hormonal replacement therapy (HRT).

The CHMP noted that the pharmacokinetic data demonstrate that estradiol is absorbed after vaginal application of Linoladiol N. Systemic effects can be expected as the estradiol levels are increased above

[4] Jain S: Dermatology, 2012, Illustrated Study Guide and Comprehensive Board Review, Springer New York

[5] Weller RPJB et al. 2008, Clinical Dermatology, Blackwell, Oxford, 4th ed.

postmenopausal levels which range from 10-20 pg/ml. Systemic levels of estradiol were of interest. Based on study SCO 5109, it is concluded that twice weekly estradiol serum levels similar to those reached with systemic hormonal replacement therapy (HRT) are observed. In addition, in study SCO 5174 it was observed that estradiol serum concentrations had not returned to baseline levels about 36 h after administration of Linoladiol N.

Comparison of pharmacokinetic data with other locally applied medicinal products was made. The CHMP noted that the maintenance dose recommended for Linoladiol N is several times higher than the maintenance dose of other estradiol containing medicinal products. An historical analysis of PK data of estradiol after vaginal application was performed based on several published studies. Of the three comparators (vaginal tablets 10 and 25 mcg and vaginal ring) discussed, estradiol vaginal tablets 25 mcg is associated with the highest systemic exposure to estradiol and was compared to Linoladiol N. After a single dose of estradiol vaginal tablets 25 mcg, C_{max} without baseline correction was 206 pmol/l, while $C_{average}$ without baseline correction during the first 24 h was 86 pmol/l based on the studies by Notelovitz (2002) and Nilsson and Heimer (1992). In comparison, after a single dose of Linoladiol N, C_{max} without baseline correction was 393 pmol/l, $C_{average}$ without baseline correction during the first 24 h was 178 pmol/l (Lauritzen, 1992; Göres, 1995 and Mazur, 2003). Taking into account baseline corrected values, C_{max} and $C_{average}$ in the 24 h interval after drug administration were 175 pmol/l and 55 pmol/l, respectively, for estradiol vaginal tablets 25 mcg, and 331 pmol/l and 120 pmol/l, respectively, for Linoladiol N.

Despite any limitations of historical comparisons with other locally applied medicinal products, it can be concluded that exposure to estradiol after administration of Linoladiol N is considerably higher than after administration of other lower dosed estradiol products for topical intravaginal therapy. The weekly exposure is higher for Linoladiol N than with other products, and this raises safety concerns, in particular considering the potential for long-term systemic exposure in daily clinical practice. The pharmacokinetics of the dosing regimen of Linoladiol N administered on the skin of the vulva was not investigated and therefore the CHMP considered that the indication should be restricted to only vaginal treatment (and not on the skin of vulva) after a lower oestrogen treatment has failed, and the treatment duration limited to four weeks. Clear information should be reflected in the posology section.

The CHMP noted that the available data on the safety of Linoladiol is limited and no prospective evaluation of safety, in particular endometrial safety was available. In terms of pharmacovigilance data, a total of 11 cases were reported including spontaneous reports and literature cases. However, no conclusions regarding endometrial safety can be drawn based on post-marketing data, due to the low number of total reported cases for Linoladiol N and the confounded cases reporting endometrial events. In addition to endometrial safety concerns, known risks for systemic oestrogen-containing products for HRT are breast cancer, ovarian cancer, venous thromboembolism, ischaemic stroke. Therefore, the CHMP considered that given the potential risks linked with all HRT treatments, information on supervision and appropriate warnings on e.g. endometrial hyperplasia and carcinoma, breast and ovarian cancer, need to be reflected in the appropriate section of the product information.

In addition the restriction to 4 weeks use of these products is justified by the clinical data currently available. However due to no specific safety reports to-date only the well-known risks of systemic HRT are to be expected. Restriction of the indication to only intravaginal use (and not on the skin of vulva) after a lower oestrogen treatment has failed, as well limiting the duration of the treatment will better reflect the available scientific and clinical data and the current clinical knowledge on the use of topical administered estradiol containing products and Linoladiol N.

2.5.2. Linoladiol HN

The CHMP took also into account the available data for Linoladiol HN, which was limited only to postmarketing spontaneous reports. No clinical studies investigating pharmacokinetics and absorption of estradiol and prednisolone, dose or efficacy of Linoladiol HN in the therapeutic indications approved have been submitted.

Linoladiol HN contains both estradiol and prednisolone and an anti-inflammatory effect of the prednisolone on inflamed skin can be expected. Furthermore, due to the content of the corticosteroid prednisolone, use of Linoladiol HN is recommended only for short-term therapy (up to four weeks). The CHMP considered that Linoladiol HN could continue to be used in the initial short-term external treatment of acute, mild, inflamed, burning and itching skin diseases of the external female genital area, for which weak-acting corticosteroids and low-dose estradiol are indicated. In addition, the clear reference to the patient population (postmenopausal women) intended to treat should be added. In addition, the CHMP considered that the maximum duration of treatment should continue to be restricted to four weeks, and clear information that treatment beyond four weeks is not recommended should be reflected in the posology section.

Information on the safety profile of this product is limited, as there are no clinical studies performed and only post-marketing data are available.

With regards to the use of Linoladiol HN for the treatment of *lichen sclerosus genitalis,* the CHMP noted that according to the current clinical knowledge on the treatment of this condition, estradiol is not a treatment option. The CHMP therefore recommended the deletion of this indication from the product information.

In addition, although Linoladiol HN contains a lower (half) concentration of estrogen than Linoladiol N, the CHMP considered that the product information should still reflect adequate warnings with regards to risks of hormone replacement therapy. Clinical monitoring is expected and caution should be used in e.g. patients with a history of malignant estrogen-dependent tumours or tumours of the womb. Vigilance is required for possible systemic side effects and skin atrophy. Prolonged use is not recommended and skin irritation, hypersensitivity and spotting were reflected in the undesirable effects. Clarification as to the nature of the active substance, estradiol, as the most potent oestrogen and the potential effect on the skin and genetic information were also reflected in the product information, in line with current scientific knowledge.

2.5.3. Overall benefit-risk assessment

The Committee concluded that the benefit-risk balance of 0.01% w/w estradiol containing medicinal products for the short-term external treatment of vaginal atrophy in postmenopausal patients when at least one topical oestrogen treatment has failed remains positive subject to the restrictions, warnings, changes to the product information agreed.

The Committee concluded that the benefit-risk balance of 0.005 % w/w estradiol, 0.4 % w/w prednisolone containing medicinal products for topical use for the initial short-term external treatment of acute, mild, inflamed, burning and itching skin diseases of the external female genital area in postmenopausal patients, for which weak-acting corticosteroids and low-dose estradiol are indicated remains positive subject to the restrictions, warnings, changes to the product information agreed.

2.6. Re-examination procedure

Following the adoption of the CHMP opinion and recommendations during the December 2013 CHMP meeting, a re-examination request was received from one MAH. The re-examination was on the Linoladiol N medicinal product only.

It is noted that the CHMP is a scientific committee and that while it operates within the legal framework, 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 CHMP, and therefore the re-examination of the referral procedure under Article 31 of Directive 2001/83/EC focused only on the scientific grounds for re-examination.

2.6.1. Detailed grounds for re-examination submitted by the MAH

The MAH agreed to limit the maximum duration of treatment to four weeks and to restrict the route of administration to intravaginal administration only.

The MAH expressed disagreement with the CHMP opinion, focusing its grounds for re-examination on the following points in relation to Linoladiol N only.

Primarily the MAH disagreed with the recommended restriction of indication for Linoladiol N of *"Treatment of vaginal atrophy due to oestrogen deficiency in postmenopausal women when at least one lower dose topical oestrogen treatment has failed".* The MAH proposed the wording *"Treatment of vaginal atrophy due to oestrogen deficiency in postmenopausal women".*

Secondly, the MAH disagreed with the CHMP assessment of the overall profile of the Linoladiol N product. They additionally argued that the pharmacokinetic profile, the systemic exposure and the potential risks should not be evaluated in relation to systemic HRT, and that the topical use of Linoladiol N cannot be compared to the systemic HRT treatment. Thus, they disagreed with some of the amendments proposed by the CHMP to be implemented in the product information.

2.6.2. CHMP conclusions on grounds for re-examination

The CHMP re-examination assessment focused on the specific grounds for re-examination as referred above. The CHMP took into consideration again the totality of the data submitted by the MAHs in the context of the initial referral procedure and, in addition, clinical guidelines[6, 7] proposing the use of topical oestrogens after lack of/inadequate response to non-hormonal vaginal lubricants / moisturisers, and other non-hormonal interventions. High dose estradiol products such as Linoladiol N are not specifically considered in these recommendations. The CHMP noted that in postmenopausal women reporting vaginal symptoms as their only complaint, guidelines recommend that these symptoms can be safely and effectively managed with low-dose oestrogen therapy, which reduces the risks associated with long-term systemic hormone therapy. Lower oestrogen-containing products are available in the Union[8].

6 Rees et al. EMAS clinical guide: Low-dose vaginal estrogens for postmenopausal vaginal atrophy. Maturitas 2012; 73: 171–174.

7 Management of symptomatic vulvovaginal atrophy: 2013 position statement of The North American Menopause Society. Menopause, 2013. 20(9): 888-902

8 Simon, J.A and Maamari R.V. Ultra-low-dose vaginal estrogen tablets for the treatment of postmenopausal vaginal atrophy. Climacteric, 2013; 16(suppl 1):37-43

Pharmacokinetics

Systemic levels of estradiol are of importance due to well-known safety concerns. During the initial review a comparison of Linoladiol PK data with other locally applied medicinal products was made (see table 1, *Comparison of PK data for estradiol containing medicinal products for topical use (intravaginally))*.

Based on the provided comparison of the C_{max} and $C_{average}$ values for Linoladiol N, it appears that the systemic estradiol exposure at steady state (twice weekly) is approximately 2.5-3 fold higher with Linoladiol N cream compared to 10mcg tablets and about 25% higher than for the 25mcg tablets. Despite well recognised limitations of historical comparisons, it can be concluded that the systemic exposure to estradiol observed for Linoladiol N is clearly higher than those for other estradiol products intended for topical vaginal use.

Moreover, the systemic levels seen for this product with twice weekly administration appear roughly comparable to those seen for transdermal patches with a release rate of 50mcg/day estradiol or 1mg estradiol tablets, which are products in the medium range of estradiol dosing. Whether twice-weekly administration (with high oestrogen systemic exposure occurring twice a week) translates into lower risk than daily administration is currently unknown and represents an important matter of concern.

The available pharmacokinetic data demonstrate that estradiol is systemically absorbed after intravaginal application of Linoladiol N. PK data from study SCO 5174 indicate that estradiol concentrations after 6h of administration (C_{max} 92.2 pg/ml) peaked well above recommended post-menopausal levels and had not returned back to baseline levels after 36h of administration. Evidence of systemic effects after 4 weeks of treatment with Linoladiol N were seen in this pivotal study, as decreased levels of FSH and LH were observed. Although the clinical meaning of this finding is unknown, it indicates that systemic effects do indeed occur with Linoladiol N.

As vaginal atrophy in post-menopausal women, as oestrogen deficiency due to oestrogen deficiency is a chronic condition, recurrence of signs and symptoms is expected to occur when topical oestrogen therapy is withdrawn. An increase in oestrogen-related risk with recurrent use of this product cannot be ruled out and is therefore considered a potential safety risk. Keeping in mind that the systemic exposure observed for Linoladiol N is clearly higher than reported for other estradiol-containing products available for intravaginal use, restricting the duration of use to only 4 weeks is considered adequate. Based on the safety concerns with regard to the systemic estradiol exposure related with this product in the target population of post-menopausal women, the CHMP concluded that alternative treatments in line with current European and international clinical practice recommendations should be considered if symptoms reoccur after withdrawal of treatment.

In conclusion, available data indicate a clinically relevant systemic exposure to estradiol for Linoladiol N, which is clearly higher than with other intravaginally administered estradiol products. Systemic effects, such as FSH and LH decreases, were also observed as noted above. Therefore, precautionary measures and restrictions of the conditions for use, similar to those recommended for systemic HRT should apply to Linoladiol N. The CHMP considered that the product information should include recommendations according to the core SmPC for Systemic HRT (4th revision, 2012)[9]

[9] http://www.hma.eu/fileadmin/dateien/Human_Medicines/CMD_h_/Product_Information/Core_SPC_PL/Core_SPCs/CMDh-131-2003-Rev4-Clean_2012_06.pdf

Efficacy

Regarding efficacy, it can be expected that a high dose of oestrogen will be efficacious in reducing vaginal atrophy and potentially similar to that seen for other topical oestrogens. However, in view of the high systemic exposure to oestrogens achieved with Linoladiol N restricting its use to 4 weeks of duration is considered necessary in order to minimise any potential risks on the basis of the safety concerns in the target population of post-menopausal women.

The CHMP agreed with the MAH that although current clinical guidelines differentiate between systemic and topical oestrogen treatments and clearly topical treatments are recommended for this condition, they do not make a recommendation for a ranking of the different topical treatments. The CHMP therefore agreed that the proposed indication for Linoladiol N *"Treatment of vaginal atrophy due to oestrogen deficiency in postmenopausal women"* could be acceptable, provided that the duration of use of the medicinal product is limited to 4 weeks.

Safety

In terms of post-marketing safety, the absence of data on serious adverse effects from spontaneous reporting is not to be considered a reassuring argument, taking into account that significant under-reporting is expected for a product which has been available on the market for many years. Moreover, there is a long latency period for some of the known adverse events of HRT that makes an association with former use of the product and thus reporting of adverse events unlikely. Notably, no prospective evaluation of safety, in particular endometrial safety, is available.

Systemic HRT in postmenopausal women has a well-known influence on the endometrium, breast, ovaries as well as a pro-thrombotic effect. As the use of Linoladiol N results in measurable increase of serum estradiol (at least temporarily and - depending on the definition- potentially exceeding postmenopausal limits) it has the potential for systemic action. Therefore, inclusion of warnings in the product information of Linoladiol N with regard to the potential risks of systemic HRT is justified; this was already accepted by the MAH.

Other sources of post-marketing data, such as observational prospective studies are not available.

Therefore, it is not possible to confirm or to rule out the potential negative impact on endometrial safety of the high oestrogen exposure.

2.6.3. Risk minimisation measures and other activities

Other risk minimisation measures in line with those recommended for systemic HRT, are also considered necessary due to the systemic exposure seen with these medicinal products and have been already reflected in the PI, as agreed during the initial referral procedure. However, since treatment duration was restricted to 4 weeks, the need for opposed progesterone is not deemed necessary.

For 0.01% w/w estradiol containing medicinal products for topical use the CHMP noted that the current pack sizes of the products need to be reduced as currently the quantity allows for longer than the maximum of 4 weeks restricted use. So, further to the absolute limitation of duration of treatment, the CHMP requested the withdrawal of the pack sizes of 100g in all EU Members States where the products are authorised.

Moreover the MAHs have been requested to provide a detailed plan including precise short timelines on the adaptation of the lower pack size (25g) to include the applicator in the package and the withdrawal of the 35g and 50g pack sizes, in all EU member states where they are currently authorised. Thus in

combination with the reduction of the treatment duration to 4 weeks, it is considered that adequate risk minimisation measures are in place to ensure the safe use of these products.

A post-authorisation prospective drug utilisation study (DUS) for estradiol cream 0.01 % w/w medicinal products for topical use was recommended by the CHMP to confirm that the restrictions on the use of the product are followed in clinical practise. The CHMP recommended that the study assessing the effectiveness of the risk minimisation measures and the new duration of use (4 weeks, not repeated) may be performed either in different Member States or in one Member State where patient exposure is high.

2.6.4. Overall benefit-risk assessment

Current treatment guidelines for vaginal atrophy recommend the use of low dose local vaginal oestrogens, along with non-hormonal lubricants or moisturisers. Vaginal oestrogen therapy has been shown to provide improvement in the signs and symptoms of vaginal atrophy. Based on the totality of the data available on the safety and the efficacy of 0.01% w/w estradiol containing medicinal products to-date, the CHMP confirmed its initial conclusion that the benefit-risk balance remains favourable subject to the restrictions, warnings, changes to the product information, and risk minimisation measures agreed.

2.7. Changes to the product information

Several sections of the product information for both group of medicinal products were revised and information was added to reflect the current clinical knowledge for these medicinal products. Below only the most modified sections are presented, as the changes for some sections were in the interest of readability only and therefore they are not specified below.

A. For 0.01% w/w estradiol containing medicinal products for topical use

Summary of product characteristics

Section 4.1 Therapeutic indications

The indication has been modified as follows:

Treatment of vaginal atrophy due to oestrogen deficiency in postmenopausal women.

Section 4.2 Posology and method of administration

In this section it was clarified that the products should be applied only intravaginally and not on other parts of the internal genital area, as no studies have been done on other parts of internal genital areas.

The short duration of use recommended by the CHMP was emphasised in this section, as application beyond 4 weeks is not recommended, due to potential systemic exposure to estradiol during treatment. If symptoms re-appear after treatment then alternative therapies should be considered.

Section 4.3 Contraindications

The contraindications have been updated according to knowledge provided by other local hormonal treatments for the external genital area, emphasising the current scientific knowledge on oestrogen-dependent tumours as well as tumours of the womb.

Section 4.4 Special warnings and precautions for use

This section of the SmPC was updated with the current knowledge on the investigation of genital bleeding. Caution is advised when using this product in women who have undergone hysterectomy because of endometriosis, especially if they are known to have residual endometriosis. These changes reflect the current scientific knowledge on the safety of oestrogen containing topical products, and extensive information has been included in this section.

Section 4.8 Undesirable effects

This section of the SmPC was extensively amended to include the current available scientific knowledge on the safety of oestrogen containing topical products. The known risks for systemic oestrogen-containing products for HRT are breast cancer, ovarian cancer, venous thromboembolism, ischaemic stroke and extensive information has been included also in this section.

The latest Quality Review Document (QRD) template was used to re-format the information.

Section 5.1 Pharmacodynamic properties

In this section some information has been deleted as it did not reflect accurately the knowledge on the product.

Section 5.2 Pharmacokinetic properties

This section was reformatted accurately reflecting the knowledge form the clinical studies of the products.

Package Leaflet

The relevant sections of the package leaflet of these products were amended accordingly.

B. For the 0.4% w/w prednisolone and 0.005% w/w estradiol containing medicinal products

Summary of product characteristics

Section 4.1 Therapeutic indications

The indication for the 0.4% w/w prednisolone and 0.005% w/w estradiol has been modified as follows:

> *"For the initial short-term external treatment of acute, mild, inflamed, burning and itching skin diseases of the external female genital area in postmenopausal patients."*

As oestrogens are no treatment options for *lichen sclerosus genitalis* according to current text books this indication has been removed. In addition, the CHMP has recommended that the therapeutic indication should be restricted explicitly to postmenopausal patients.

Section 4.2 Posology and method of administration

In this section it was clarified that the products should not be applied intravaginally or on other parts of the internal genital area, as no studies have been done on intravaginal application or other parts of internal genital areas.

The short duration of use recommended by the CHMP was emphasised in this section, as application beyond 4 weeks is not recommended, due to potential systemic exposure to estradiol during treatment. In addition, due to the content of the corticosteroid prednisolone in Linoladiol HN, skin atrophy might occur with prolonged use, and further increasing systemic exposure to estradiol.

Section 4.3 Contraindications

The contraindications have been updated according to knowledge provided by other local hormonal treatments for the external genital area, emphasising the current scientific knowledge on oestrogen-dependent tumours as well as tumours of the womb.

Section 4.4 Special warnings and precautions for use

This section of the SmPC was updated with the current knowledge on the investigation of genital bleeding. Caution is advised when using this product in women who have undergone hysterectomy because of endometriosis, especially if they are known to have residual endometriosis. Also information was added taking into consideration the current clinical knowledge on safety of systemic HRT especially regarding thromboembolism and breast and endometrial cancer.

Section 4.6 Pregnancy and lactation

This section of the SmPC was brought in line with the safety information on the use of oestrogen during pregnancy and lactation.

Section 4.8 Undesirable effects

This section of the SmPC was updated with the information of possible systemic exposure and restriction to four weeks of use.

Section 5.1 Pharmacodynamic properties

In this section information has been deleted as it did not reflect accurately the knowledge on the product.

Section 5.2 Pharmacokinetic properties

The information that no clinical studies have been performed on the dermal absorption of these products has been included.

B. Package Leaflet

The relevant sections of the package leaflet of these products were amended accordingly.

3. Overall conclusion and grounds

Having considered the overall submitted data provided by the MAHs in writing and in the oral explanations and having considered relevant scientific guidance and recommendations providing for the standard of care in the relevant field, the CHMP revised its opinion and recommended the variation to the terms of the marketing authorisation for the medicinal products referred to in Annex I of the CHMP opinion for which the relevant sections of the summary of product characteristics and package leaflet are set out in Annex III of the opinion, and subject to the conditions set out in Annex IV of the opinion.

Whereas

- The Committee considered the procedure under Article 31 of Directive 2001/83/EC of the 0.01% w/w estradiol containing medicinal products for topical use as well as fixed dose combination products containing 0.005 % w/w estradiol with 0.4 % w/w prednisolone for topical use.
- The Committee reviewed all available data from clinical studies, pharmacoepidemiological studies, published literature, post-marketing experience, including responses submitted by the marketing authorisation holders (MAHs) in writing and at oral explanations, on the efficacy and safety of these medicinal products for topical use.
- For the 0.01% w/w estradiol containing medicinal products for topical use the Committee considered that in view of the currently available data, the benefit-risk balance remains favourable in the currently authorised indication, subject to restrictions, warnings and other changes to the product information, as well as further risk minimisation measures agreed. In particular, the treatment applies to vaginal atrophy in postmenopausal women, duration of treatment should be limited to four weeks and the product is intended for intravaginal administration only. In addition, the contraindications and warnings have been updated to take into consideration the international guidelines and current clinical knowledge on safety of systemic HRT especially regarding thromboembolism and breast and endometrial cancer, and also the known lack of sensitivity of spontaneous adverse event reporting.
- The Committee, in order to ensure that the 0.01% w/w estradiol containing medicinal products for topical use are not used for periods longer than 4 weeks, imposed the withdrawal of pack size of 100g in all EU Members States where the products are authorised. In addition the MAHs have been requested to provide a detailed plan including precise short timelines on the adaptation of the lower pack size (25g) and the withdrawal of the 35g and 50g pack sizes, in all EU member states where they are currently authorised.
- For the 0.005 % w/w estradiol with 0.4 % w/w prednisolone containing medicinal products for topical use the Committee considered that in view of the currently available safety data these products should be used for the initial short-term external treatment of acute, mild inflammatory skin diseases of the external genital area in postmenopausal women for which weak acting corticosteroids and estradiol are indicated. Restrictions, warnings and other

changes to the product information were proposed to reflect current clinical knowledge on the safety of HRT especially regarding thromboembolism, and breast and endometrial cancer.

- The Committee is of the opinion that the benefit does not outweigh the risks in the indication of *lichen sclerosus genitalis* for the 0.005 % w/w estradiol with 0.4 % w/w prednisolone containing medicinal products, in line with current clinical knowledge and therefore this indication should be deleted.

The Committee, as a consequence, concluded that the benefit-risk balance of the 0.01% w/w estradiol containing medicinal products for topical use as well as the 0.005 % w/w estradiol and 0.4 % w/w prednisolone containing medicinal products for topical use remains favourable subject to variation to the term of the marketing authorisation consisting of restrictions, warnings, and other agreed changes to the product information, and the risk minimisation measures agreed, as applicable.