Annex II

Scientific conclusions and grounds for the variation to the terms of the marketing authorisations

Scientific conclusions

Overall summary of the scientific evaluation of high concentration estradiol containing medicinal products for topical use

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 these 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.

0.01 % w/w estradiol containing medicinal products for topical use (Linoladiol N)

The CHMP took into account all available data on pharmacokinetics (PK), 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) in the approved therapeutic indication.

The main studies supporting intravaginal application are Studies SCO 5109 and SCO 5174.

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. The primary objective of the study was to estimate the extent of estradiol exposure after application of the test formulation 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 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 6 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 10.7 pg/ml.

Study SCO 5174, 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 regard 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 this study, 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.

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

The CHMP noted that the pharmacokinetic data demonstrate that estradiol is absorbed after vaginal application of the Linoladiol N. Systemic effects can be expected as the estradiol levels are increased above postmenopausal levels which range from 10-20 pg/ml.[1]

Systemic levels of estradiol in these two studies raised concerns. 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 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 about 8 times higher than the maintenance dose of estradiol 25 mcg vaginal tablets and estradiol vaginal ring and 20 times higher than the maintenance dose of estradiol 10 mcg vaginal tablets.

The CHMP agreed with the MAH that not only dose, but also absorption and systemic concentrations of topically administered estradiol are of interest. An historical analysis of pharmacokinetic data of estradiol after vaginal application across several published studies has been performed. 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, regarding estradiol vaginal tablets 25 mcg, and 331 pmol/l and 120 pmol/l, respectively, regarding 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,

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

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 and the known lack of sensitivity of spontaneous reporting, 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.

0.005 % w/w estradiol/0.4 % w/w prednisolone containing medicinal products for topical use (Linoladiol HN)

The CHMP took also into account the available data for Linoladiol HN, which was limited mainly to post-marketing data. No clinical studies investigating PK/absorption of estradiol and prednisolone, dose-finding and the 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.

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 oestrogen 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 oestrogen-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.

Overall benefit-risk balance

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.

Re-examination procedure

Following the adoption of the CHMP opinion and recommendations during the December 2013 CHMP meeting, a re-examination request on Linoladiol N medicinal product only was received from one 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 which addresses the concerns regarding long term exposure data and missing study data in question of treatment of skin of the vulva.

There were two main scientific points of disagreement with the CHMP opinion addressed in the MAH's grounds for re-examination.

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 favoured the initial indication of *"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 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 systemic HRT treatment. Thus, they disagreed with some of the amendments proposed by the CHMP to be implemented in the product information.

The CHMP conclusions on these points raised in the MAH's grounds are given below.

The CHMP carried out a new assessment of the available efficacy data in the concerned indication. In particular, the CHMP re-assessed the pharmacokinetic data available, as well as the comparison to existing treatments in consultation to the international guidelines.

Clinical guidelines[2,3] propose 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 authors state that in postmenopausal women reporting vaginal symptoms as their only complaint, these symptoms can be safely and effectively managed with low-dose oestrogen therapy, which reduces the risks associated with long-term systemic hormone therapy.

In terms of the PK data, systemic levels of estradiol are of interest due to well-known safety concerns. During the referral procedure a comparison of Linoladiol N available PK data with other locally applied medicinal products was made. In this comparison, three other intravaginally applied medicinal products were included: 10 mcg and 25 mcg vaginal tablets, and 2 mg vaginal ring. Based on the provided comparison of the C_{max} and $C_{average}$ values for Linoladiol N, it appears that the systemic exposure to estradiol at steady state (twice weekly) is about 2.5-3 fold higher compared to 10mcg tablets and about 25% higher for Linoladiol N cream than for the 25 mcg tablets. Despite any limitations due to the historical comparisons, it can be concluded that the systemic exposure to estradiol observed for

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

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

Linoladiol N is higher than those for other estradiol products intended for topical vaginal use. The systemic levels seen for this product with twice weekly administration are comparable to those seen for 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) peak well above recommended post-menopausal levels and had not returned back to baseline levels after 36h of administration (likely reflecting trough levels). Decreases in FSH and LH were also observed, further reflecting the existence of relevant systemic exposure.

Since the systemic exposure observed for Linoladiol N is much higher than those reported for other estradiol-containing products available for intravaginal use, restricting the duration of treatment to four weeks is considered an adequate risk minimisation measure given the existing safety concerns and the surrounding uncertainties regarding the systemic estradiol exposure related with this product in the target population of post-menopausal women.

Systemic exposure is neither required nor advised for topical therapy and raises known safety concerns recognized for systemic HRT. Based on the higher dose and substantial systemic estradiol exposure this product is more comparable to systemic HRT products from a safety point of view. As vaginal atrophy due to oestrogen deficiency in post-menopausal women is a chronic condition, recurrence of signs and symptoms is expected when topical oestrogen therapy is withdrawn. An increase in oestrogen-related risk with recurrent use of this product cannot be ruled out. For that reason the CHMP recommended to restrict the use of these medicinal products to 4 weeks only (no repeated use), and advised that if symptoms of vaginal atrophy re-appear alternative therapies, either non-hormonal or lower-dose estradiol containing topical products, should be considered.

The Committee accepted the MAH's argument 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. Thus, a second line indication as proposed in the initial CHMP opinion i.e. the use of Linoladiol N after low-dose topical estradiol treatment has failed, although intended, is not explicitly stated in the international guidelines. The Committee therefore agreed that the indication could be *"Treatment of vaginal atrophy due to oestrogen deficiency in postmenopausal women",* according to the MAH grounds, provided that a restriction on the duration of use of these medicinal products to 4 weeks only (not repeated use), as mentioned above.

In order to enforce this short duration of use, the CHMP requested withdrawal of the pack sizes of 100 g in all EU Members States where the products are authorised, as this large pack size of cream is considered redundant under the new recommendations for the duration of use. In addition for further minimisation of any potential safety risk, the MAHs have been requested to provide a detailed plan including precise short timelines on the adaptation of the lower pack size (25 g) to add an applicator in the package and the withdrawal of the 35 g and 50 g pack sizes, in all EU member states where they are currently authorised.

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 that the benefit-risk balance remains favourable subject to the restrictions, warnings, changes to the product information, and risk minimisation measures agreed.

Grounds for the variation to the terms of the marketing authorisations

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 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 is 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 100 g 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 (25 g) and the withdrawal of the 35 g and 50 g 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 risk 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 changes to the product information, as well as the risk minimisation measures agreed, as applicable.