LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Estradiol SUN
(estradiol hemihydrate)

SE/H/2050/01/DC

This module reflects the scientific discussion for the approval of Estradiol SUN. The procedure was finalised on 2021-01-18. For information on changes after this date please refer to the module 'Update'.

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I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, a marketing authorisation has been granted for Estradiol SUN, 10 microgram, Vaginal tablet.

The active substance is estradiol hemihydrate. A comprehensive description of the indication and posology is given in the SmPC.

For recommendations to the marketing authorisation not falling under Article 21a/22a/22 of Directive 2001/83/EC and conditions to the marketing authorisation pursuant to Article 21a/22a/ 22 of Directive 2001/83/EC to the marketing authorisation, please see section VI.

The application for Estradiol SUN, 10 microgram, vaginal tablet, is submitted according to Article 10a of Directive 2001/83/EC. The applicant, Sun Pharmaceutical Industries Europe B.V. applies through the Decentralised Procedure with Sweden acting as reference member state (RMS) and IE, UK as concerned member states (CMS).

For an application according to Article 10a, WEU, the applicant needs to demonstrate that the active substance of the medicinal product has been in well-established medicinal use for the claimed therapeutic indication within the Union for at least ten years, with recognised efficacy and an acceptable level of safety.

The applicant has justified well-established medicinal use as follows;

“Active substance of the medicinal product has been in well-established medicinal use within the Community for at least 10 years

Applicant’s Estradiol SUN vaginal tablets 10 µg contain oestrogen indicated for the treatment of vaginal atrophy due to oestrogen deficiency in postmenopausal women.

- Oestrogen has been approved for systemic use as hormone replacement therapy and has been in well-established medicinal use within community for more than 20 years since November 1996.
- Other local vaginal oestrogen formulations such as creams/gels/rings etc have been approved and in use in European community for more than 23 years for treatment of atrophic vaginitis (due to estrogen deficiency) in post-menopausal women.
- The proposed Estradiol SUN 10 mcg vaginal tablets are similar to already approved VAGIFEM 10 µg of Novo Nordisk that have been in clinical use since 2010 and estradiol tablets have been in use more than 20 years.”

In support of the application, the Applicant has submitted published literature and a supportive clinical study. The provided review of published clinical data on clinical pharmacology, efficacy and safety submitted in support of the present application is considered acceptable.

In the RMS opinion, the clinical efficacy of estradiol administered as vaginal tablets is well-established. The innovator product Vagifem® has been marketed since 2010 as a 10 µg strength, and for over 25 years as the previous strength of 25 µg. Well-established medicinal use for the claimed therapeutic indication within the Union for at least ten years, with recognised efficacy and an acceptable level of safety, has been shown.

The active substance is not considered a new active substance.

Potential similarity with orphan medicinal products

According to the application form and a check of the Community Register of orphan medicinal products there is no medicinal product designated as an orphan medicinal product for a condition relating to the indication proposed in this application.

II. QUALITY ASPECTS

II.1 Drug Substance

The structure of the drug substance has been adequately proven and its physico-chemical properties are sufficiently described.

The manufacture of the drug substance has been adequately described and satisfactory specifications have been provided for starting materials, reagents and solvents.

The drug substance specification includes relevant tests and the limits for impurities and degradation products have been justified. The analytical methods applied are suitably described and validated.

Stability studies confirm the retest period.

II.2 Medicinal Product

The medicinal product is formulated using excipients listed in section 6.1 in the Summary of Product Characteristics.

The manufacturing process has been sufficiently described and critical steps identified.

The tests and limits in the specification are considered appropriate to control the quality of the finished product in relation to its intended purpose.

Stability studies have been performed and data presented support the shelf life and special precautions for storage claimed in the Summary of Product Characteristics, sections 6.3 and 6.4.

III. NON-CLINICAL ASPECTS

Pharmacology
The influence of estrogens on several body systems and especially the reproductive tissues, has been well documented. Estrogen works mainly through its two distinct nuclear receptors, Estrogen Receptor alpha (ERα) and Estrogen Receptor beta (ERβ). Binding of estrogens to these receptors leads to transcriptional activation of estrogen-responsive genes and subsequent modification of cellular responses.
17β-Estradiol (which is the estrogen of relevance for the present product) is the major estrogen secreted by the premenopausal ovary and acts as a growth hormone for female reproductive organs including the vaginal lining, cervical glands, lining of the fallopian tubes, the endometrium, and the myometrium. Effective treatment of vulvovaginal atrophy by vaginal estradiol formulations have been demonstrated by effects on maturation of the vaginal epithelium, effects on vaginal pH and on the endometrium. The pharmacology studies presented by the Applicant are overall considered sufficient for this Application.

Pharmacokinetics
Oral administration of estrogens is associated with substantial first-pass effect, limiting the bioavailability. After vaginal administration, estradiol is well absorbed through the vaginal epithelium and circumvents the “first pass” hepatic metabolism.

Toxicology
A full programme of toxicity studies has been referenced by the Applicant. Estradiol has been in clinical use for many years and its clinical safety profile is well-known. Repeated-dose toxicity studies

in rats and rabbits have been referenced by the Applicant. Weight-loss is a prominent clinical sign of estrogens at high doses. Further, effects in lymphoid organs, haematology parameters and reproductive organs were frequently seen. Overall, these effects are considered well-known and are expected based on the pharmacology of estrogens.

The mutagenic activity of estadiol was evaluated in a number of Ames tests. Collectively, it was concluded that estradiol is not mutagenic. Further, chromosomal aberrations were assessed in Syrian hamster embryo cells. Estradiol did not induce chromosomal aberrations in this assay. Finally, estradiol was evaluated in five tests for the induction of micronuclei in bone marrow in vivo. Estradiol given as three daily subcutaneous doses of 20 μg/kg bw and in mice given a single intraperitoneal injection of 10-150 mg/kg bw. was not genotoxic to the bone marrow.

Carcinogenicity studies in mice and Syrian hamsters showed that estradiol is carcinogenic. Based on its lack of mutagenic activity in bacterial and mammalian cell test systems, several epigenetic mechanisms of tumour induction by this hormone have been proposed. Estradiol is classified as carcinogenic to humans (Group 1).

The Applicant has provided with data from several DART studies in mice and rats. In one study, estradiol administered to female Crl:CD BR rats at doses equal to 0, 0.003, 0.17, 0.69, or 4.1 mg/kg bw per day in a 90-day study, showed that no pups were born in the two highest dose-groups. Further, pup-weights were reduced in the remaining groups, which may be related to the decreased gestation length relative to controls. In addition, sexual maturity was delayed in juveniles of both sexes. Collectively, the studies suggest that high doses of estradiol may have developmental effects in rats and mice. Given that Estradiol SUN is indicated in post-menopausal women only, the reproductive effects are of minor relevance for this product.

Environmental Risk Assessment (ERA)

An ERA for estradiol has been submitted, in which a PEC-value for surface water has been calculated. Further, consumption data for the RMS (SE) and CMS (UK and IE) from the IMS database for the past 4 years has been provided. For EAS substances, a Phase II assessment should normally be performed irrespective of the PEC action limit and studies on environmental fate are also required for all EAS.
However, considering that estradiol is a well-established substance (and EAS), no new or additional ERA-studies are considered needed. It is also noted that section 6.6 has been updated with a statement that 17β-estradiol is expected to pose a risk to the aquatic environment, especially to fish populations. This is endorsed.

IV. CLINICAL ASPECTS

Pharmacokinetics
After vaginal administration, estradiol is well absorbed through the vaginal epithelium and circumvents the “first pass” hepatic metabolism noted with oral administration. A 12 week study comparing 10 μg with 25 μg vaginal tablets concluded that 10 μg vaginal tablets resulted in at least 50% lower mean estradiol concentrations than with the 25 μg dose within 24 h after dosing. Administering the 25 μg dose, mean estradiol (E2) levels during the first 2 weeks exceeded the published reference range for postmenopausal women, while, with the 10 μg dose, mean E2 levels remained in that range from the beginning, indicating minimized estradiol absorption. The systemic levels of estradiol have been reported to be within the normal untreated menopausal range after 1 year of twice-weekly treatment with the 10 μg E2 vaginal tablet. Overall, systemic absorption of E2 was low and stable. In conclusion, systemic oestrogen exposure with the ultra-low-dose 10 μg E2 vaginal tablet is minimal; this significantly reduces the likelihood of occurrence of clinically relevant systemic side-effects.

Estrogens are highly protein bound. Although some estrogens are loosely bound to albumin, the

majority of estradiol is tightly bound to sex hormone binding globulins. Estrogens are eliminated from the body by metabolic conversion to estrogenically inactive metabolites that are excreted in the urine and/or faeces.

The pharmacokinetic profile of vaginal estradiol reveals that there is very low systemic absorption of estradiol and thus it seems unlikely that any clinically relevant drug interactions will occur with vaginal tablets. However, published literature has reported interactions with systemic use of oestrogen.

The Applicant has submitted one clinical bioequivalence study (study PKD-13-052) as supportive bridging data:

Bioequivalence study PKD 13 052

A randomized, open-label, two-treatment, tree period, three sequence, single-dose, reference-replicated cross-over bioequivalence study was performed in 52 healthy postmenopausal female subjects under fasting conditions subjects to compare the test product Estradiol 10 µg vaginal tablets by Sun Pharmaceuticals with the reference product Vagifem 10 µg vaginal tablets. A wash out period of 10-11 days was held between the treatment periods.

The reference product was obtained from USA. The qualitative composition is identical and according to reverse engineering the quantitative composition is comparable and seems to be identical between the US and EU reference product. The study was conducted during 15 July and 14 August 2013 at Sun Pharmaceuticals Industries Tandalja, Vadodara, India. Forty-six (46) subjects completed all three periods of the study. A validated LC/MS/MS bioanalytical method was used for quantification of estradiol in plasma. Baseline correction for endogenous estradiol levels was performed.

The 90% confidence intervals are calculated and presented below.

SUMMARY OF STATISTICAL ANALYSIS OF ESTRADIOL [With baseline correction]

Ln- Transformed Data

PK Variables	Least Squares Geometric Means[3]				Ratio of Least-Squares Geometric Means[1] %	Reference Intra-subject CV %	90% Geometric C.I.[2]	BE acceptance limit
	Test	N	Reference	N				
AUC_{0-t}	103.33	46	98.25	47	105.17	81.50	84.86 to 130.35	80.00 to 125.00
C_{max}	18.28	46	15.53	47	117.69	63.78	98.73 to 140.29	69.84 to 143.19

N= number of subjects **Source: Annexure - 2**

1 Calculated using least square means according to the formula: $e^{(LSM\ Treatment\ (A) - LSM\ Treatment\ (B)} \times 100$

2 90% Geometric Confidence Interval using In-transformed data;

3 Least-square geometric means calculated from least-square mean as $e^{(least\text{-}square\ mean)}$

The study PKD_13_052 was designed and conducted according to FDA guidelines, where 95% upper confidence bound criteria was applied for statistical analysis. The statistical analysis to calculate 90% confidence interval on baseline corrected individual pharmacokinetic parameters as per EMA guidance (CPMP/QWP/EWP/1401/98 Rev 1) was performed afterwards and hence the sample size have probably not been optimal to demonstrate bioequivalence.

The ratios of the least-square geometric means (and 90% geometric confidence intervals) of the test to reference product (A/B) for baseline corrected estradiol were 105.17% (84.86 to 130.35) % for AUC_{0-t} and 117.69% (98.73 to 140.29) for C_{max}, respectively, and bioequivalence was not demonstrated in the study. Since this study was submitted only as supportive study and Estradiol SUN is administered intravaginally and is locally acting, lack of demonstrating bioequivalence is acceptable.

In vitro comparison data

The two submitted studies PKD-13-052 (bioequivalence study) and study 71342602 (therapeutic equivalence study) were performed with the reference product Vagifem from the US market. The applicant has compared the innovator product Vagifem from the EU market and Vagifem from US

market. The qualitative compositions of EU and US Vagifem are identical. The Applicant has also compared the quantitative compositions of EU and US Vagifem using reverse engineering analysis. Based on this analysis the quantitative compositions of EU and US Vagifem are comparable and seem to be identical.

In Estradiol SUN, the only difference in the stated qualitative composition is in the coating where Opadry Clear 04F590001 (consisting of hypromellose E15 and polyethylene glycol 6000) is used instead of hypromellose and polyethylene glycol listed for EU and US Vagifem.

In addition, *in vitro* dissolution data comparing Estradiol SUN with Vagifem has been submitted by the Applicant within Module 3. The dissolution data can be considered as supportive bridging data for this application.

Pharmacodynamics

The clinical experience with exogenous treatment with oestrogens to treat postmenopausal vulvovaginal atrophy is extensive.

The primary pharmacodynamic effect of estradiol is maturation of the vaginal epithelium (decrease in the number of basal/parabasal and increase in superficial and intermediate cells), effect on vaginal pH and on the endometrium. The Clinical Overview provided by the Applicant contains an adequate and thorough review of the published scientific data on pharmacodynamics of estradiol.

Local vaginal administration of the 10 μg dose, as in Estradiol SUN, seem to be the lowest effective dose in alleviating postmenopausal urogenital symptoms. This dose causes only a minimal rise in serum estradiol, which remains well within the normal postmenopausal range.

Clinical efficacy

Since this is a well-established use application, adequately justified by the applicant in the Clinical Overview (see below), the application should be based on published literature.

“Active substance of the medicinal product has been in well-established medicinal use within the Community for at least 10 years

Applicant’s Estradiol SUN vaginal tablets 10 μg contain oestrogen indicated for the treatment of vaginal atrophy due to oestrogen deficiency in postmenopausal women.

- Oestrogen has been approved for systemic use as hormone replacement therapy and has been in well-established medicinal use within community for more than 20 years since November 1996.
- Other local vaginal oestrogen formulations such as creams/gels/rings etc have been approved and in use in European community for more than 23 years for treatment of atrophic vaginitis (due to estrogen deficiency) in post-menopausal women.
- The proposed Estradiol SUN 10 mcg vaginal tablets are similar to already approved VAGIFEM 10 μg of Novo Nordisk that have been in clinical use since 2010 and estradiol tablets have been in use more than 20 years.”

The published literature search strategy was presented and found to be acceptable.

The clinical efficacy of estradiol administered as vaginal tablets is well-established. The innovator product Vagifem® has been marketed since 2010 as a 10 μg strength, and for over 25 years as the previous strength of 25 μg.

The provided review of published clinical data on clinical pharmacology, efficacy and safety submitted in support of the present application is considered acceptable. Results obtained with the

estradiol 25 µg vaginal tablet is not assessed since this application concerns 10 µg estradiol formulated as a vaginal tablet.

In one report, the efficacy of the dose 10 µg 17-beta-estradiol vaginal tablets for treatment of vaginal atrophy was evaluated. Primary efficacy endpoints included change from baseline to week 12 in vaginal cytology, vaginal pH, and most bothersome urogenital symptoms score. The change from baseline at week 12 for 10 µg E2 compared with placebo showed significant improvements in vaginal maturation index (proportion of parabasal cells: -37% compared with -9%; superficial cells: 13% compared with 4%; intermediate cells: 24% compared with 5%; P<0.001 for each), maturation value (25.0 compared with 6.5, P<0.001), grading of vaginal health (-0.91 compared with -0.51, P<0.001), vaginal pH grade (-1.3 compared with -0.4, P<0.001), and most bothersome symptoms score (-1.23 compared with -0.87, P=0.003).

For each component of vaginal maturation index, vaginal maturation value, grading of vaginal health, and vaginal pH, treatment effects were statistically different from placebo after 2 weeks of treatment. For most bothersome symptoms, treatment effect became apparent after 4 weeks and reached statistical significance at week 8 of therapy. All treatment effects were statistically significant at week 52. There were no major safety findings regarding physical, gynaecologic, or laboratory assessments.

In another study, they evaluated the efficacy of two vaginal doses of estradiol (25 µg or 10 µg) E2 compared with placebo in the treatment of atrophic vaginitis. Efficacy was measured through composite score of three vaginal symptoms (dryness, soreness, and irritation) and grading of vaginal health. After 12 weeks of treatment, all patients were switched to the open-label extension and received treatment with 25 µg E2 up to week 52. Vaginal tablets with 25 µg and 10 µg E2 showed significant (P<0.001) improvement in composite score of vaginal health. The efficacy was maintained to week 52 with 25 µg E2. It was concluded that vaginal tablets with 25 µg and 10 µg E2 provided relief of vaginal symptoms, improved urogenital atrophy, decreased vaginal pH, and increased maturation of the vaginal and urethral epithelium. Those improvements were greater with 25 µg than with 10 µg E2.

A tendency for higher relief of vulvovaginal symptoms was noted in a small study in patients treated twice weekly with 25 µg 17beta-estradiol compared with once weekly treatment.

Vaginal tablets are easier to use than vaginal cream formulations, and overall more tablet users (69%) than cream users (14%) were satisfied with this mode of dose administration.

The Applicant has submitted one clinical therapeutic equivalence study (study 71342602) as supportive bridging data. Demonstrating therapeutic equivalence between the applied product and innovator product is not a requirement for an application pursuant to Article 10a of the Directive 2001/83/EC. Taking into account the totality of submitted data, it is considered that the Applicant has sufficiently well demonstrated that the published clinical data on Vagifem® is relevant also for the applied product Estradiol SUN. Moreover, the proposed clinical efficacy sections of the SmPC for Estradiol SUN are identical to the SmPC for the recently approved product Menovag® (FI/H/1014/01/DC).

Clinical safety

The Clinical Overview provided by the Applicant contains an adequate and thorough review of the published scientific data on clinical safety of estradiol. Various formulations of estradiol have been in clinical use for treatment of vulvovaginal atrophy for decades and the safety profile is considered well known. The proposed dose for marketing, estradiol 10 µg is the lowest dose effective dose with a fairly benign safety profile.

In the supportive clinical study 71342602 on therapeutic equivalence, a comparable safety profile with the innovator product Vagifem® 10 µg vaginal tablet was observed. Vagifem® 10 µg vaginal tablet

was marketed in 2010, and well-established use to this product has been shown. A considerable amount of safety data is also available for the 25 µg estradiol vaginal tablet which is no longer available on the Swedish market.

The safety sections of the proposed SmPC for Estradiol SUN are identical to the recently approved product Menovag® (FI/H/1014/01/DC) and is accepted.

Risk Management Plan

The MAH has submitted a risk management plan, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Estradiol SUN.

Safety specification
The proposed safety concerns (RMP Part II: Module SVIII) can be seen in the table below.

Summary of safety concerns	
Important identified risks	None
Important potential risks	None
Missing information	None

Pharmacovigilance Plan

Routine pharmacovigilance is suggested, and no additional pharmacovigilance activities are proposed by the applicant, which is endorsed.

Risk minimisation measures
Routine risk minimisation is suggested, and no additional risk minimisation activities are proposed by the applicant, which is endorsed.

Summary of the RMP
The submitted Risk Management Plan, version 0.2 signed 21-July-2020 is considered acceptable.

V. USER CONSULTATION

The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The language used for the purpose of user testing the PIL was English.
The results show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

From the clinical point of view, the pharmacology, efficacy and safety of estradiol hemihydrate administered as vaginal tablets is well-established. The innovator product Vagifem® has been marketed since 2010 as 10 µg strength, and for over 25 years as the previous strength of 25 µg. The provided review of published clinical data on clinical pharmacology, efficacy and safety is considered appropriate.

The Applicant has submitted one clinical therapeutic equivalence study (study 71342602) as supportive bridging data. Demonstrating therapeutic equivalence between the applied product and innovator product is not a requirement for an application pursuant to Article 10a of the Directive 2001/83/EC. Taking into account the totality of submitted data, it is considered that the Applicant has sufficiently well demonstrated that the published clinical data on Vagifem® is relevant also for the applied product Estradiol SUN.

The benefit risk of Estradiol SUN is considered positive. The application is recommended for approval.

List of recommendations not falling under Article 21a/22a/22 of Directive 2001/83/EC in case of a positive benefit risk assessment

N/A

List of conditions pursuant to Article 21a/22a or 22 of Directive 2001/83/EC

N/A

VII. APPROVAL

The decentralised procedure for Estradiol SUN, 10 microgram, Vaginal tablet was positively finalised on 2021-01-18.

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Public Assessment Report – Update

Procedure number*	Scope	Product Information affected (Yes/No)	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse

*Only procedure qualifier, chronological number and grouping qualifier (when applicable)

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