LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Vagidonna
(estradiol hemihydrate, estradiol)

SE/H/1959/01/DC

This module reflects the scientific discussion for the approval of Vagidonna. The procedure was finalised on 2020-03-15. For information on changes after this date please refer to the module 'Update'.

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I. INTRODUCTION

Sandoz has applied for a marketing authorisation for Vagidonna, vaginal tablet 10 µg. The active substance is estradiol hemihydrate, estradiol, in a vaginal tablet that has been developed for treatment of vaginal atrophy (VA) in postmenopausal women.

For approved indications, see the Summary of Product Characteristics.

The marketing authorisation has been granted pursuant to Article 10(3) of Directive 2001/83/EC.

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

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

III.1 Introduction

Estradiol hemihydrate is a widely used, well-known active substance. Pharmacodynamic, pharmacokinetic and toxicological properties of Vagidonna are well known.

III.2 Ecotoxicity/environmental risk assessment

It can be concluded that the introduction of Vagidonna on the market is unlikely to result in an increased environmental exposure to estradiol. The information on environmental risk is provided in the SmPC section 6.6.

IV. CLINICAL ASPECTS

IV.1 Introduction

IV.2 Pharmacokinetics

Systemic exposure of estradiol was assessed in a separate PK group (n=28), in the therapeutic equivalence study. PK parameters were calculated both based on the original data and after baseline correction. Pharmacokinetic data are used to extrapolate systemic safety from the reference product. Plasma exposure was evaluated at steady-state following the 14 days initial phase of daily administration, which is an acceptable approach to establish that plasma exposure is not higher for the test than for the reference product. Analysis of baseline corrected concentrations is adequate given that estradiol is an endogenous substance.

Before baseline correction, geometric mean $C_{max,ss}$-values were 10.59 pg/ml for test and 11.87 pg/ml for reference, i.e. within the normal range of endogenous estradiol levels in postmenopausal women (< 20 pg/ml).

Baseline corrected geometric mean $AUC_{0\text{-}tau}$ and $C_{max,ss}$-values were 77.89 h*pg/ml and 6.79 pg/ml respectively for the test product and 101.50 h*pg/ml and 7.84 pg/ml for the reference. For a hybrid application of a locally acting, locally applied product for which an evaluation of systemic exposure is required, it should be demonstrated that the systemic exposure is not higher than for the reference product. It is usually recommended that the upper limit of the 90% confidence interval of the test/reference ratio for AUC and C_{max} does not exceed the upper bioequivalence limit of 125.00%.

Table 1: Parametric point estimates and 90 % confidence intervals determined for selected pharmacokinetic parameters of estradiol, 10 µg per treatment, comparison Test vs. Reference

Parameter	Obser-vations	Effect	Test	Reference	Point Estimate	Lower _Limit _CI	Upper _Limit _CI	CV total	Significant _Effects	Residual Variance
AUC_TAU	27	Treatment	Test	Reference	76.74	56.76	103.74	48.34		0.21002837
AUC_last	27	Treatment	Test	Reference	76.32	56.48	103.12	48.25		0.20931205
C_max,ss	27	Treatment	Test	Reference	86.64	62.31	120.48	53.42		0.25105502

The point estimates are below 100%, indicating an observed lower systemic exposure for the test product than for the reference product. The upper limit of the 90% confidence intervals are also below the usual limit of 125.00% and hence it can be concluded that the systemic exposure is not higher by a significant amount.

IV.3 Pharmacodynamics

Estradiol (oestradiol, 17β-estradiol) is the most active of the naturally occurring oestrogens. The established benefits of oestrogen therapy in postmenopausal women include improvement of vasomotor symptoms and symptoms of urogenital atrophy. When oestrogens

are being used solely for relief of vulvar and vaginal atrophy, vaginal administration is the optimal route.

Vaginal atrophy may often lead to a reduced quality of life because of issues related to general vaginal discomfort as well as pain and bleeding during sexual activity. Additionally, the vaginal pH becomes less acidic, altering the normal vaginal flora, with the vaginal and bladder epithelium becoming more susceptible to infection and inflammation.

A low-dose oestrogen vaginal tablet containing 25 micrograms 17β-estradiol (Vagifem; Novo Nordisk A/S, Bagsvaerd, Denmark) was first introduced in 1988 and shown to provide continuous release of estradiol in an atrophic vaginal vault, with transient absorption being significantly reduced after maturation of the epithelium. It was subsequently demonstrated that a lower-dose tablet containing 10 micrograms estradiol was also effective for the relief of vaginal atrophy symptoms.

Oestrogens exert their effects by interaction with receptors that are members of the superfamily of nuclear receptors. In the atrophic vaginal mucosa, the pH is high and parabasal cells predominate. Locally administered estradiol exerts its effect on the vagina by lowering pH, increasing the number of intermediate and superficial vaginal cells and lowering of the number of parabasal cells. The effects on the vaginal mucosa of vaginal administration of estradiol are well established. As this is a local treatment with local effects, plasma concentrations of estradiol are only relevant for safety reasons and should ideally be below detection.

IV.4 Clinical efficacy

After the menopause, as a result of cessation of ovarian oestrogen production, many women develop vaginal atrophy, which may be clinically bothersome and lead to a reduced quality of life. For relief of bothersome symptoms, vaginal estradiol has long been available for clinical use and marketed since more than 20 years in many countries worldwide.

The estradiol 10 µg vaginal tablets, as in Vagidonna, may be considered a generic medicinal product equivalent to the estradiol 10 µg vaginal tablets originator products, marketed in many countries under several brand names, including Vagifem®.

The registration strategy for this product is based on Scientific Advice from MHRA/UK. A therapeutic equivalence trial was designed and conducted to evaluate the efficacy and safety of the newly developed low-dose estradiol vaginal tablet (10 µg) in postmenopausal women with vaginal atrophy in comparison to the Reference product Vagifem® (Novo Nordisk).

The applicant´s original application concerned the indication: *Treatment of vaginal atrophy due to oestrogen deficiency in postmenopausal women (see section 5.1). The experience treating women older than 65 years is limited.* After the first round the indication was amended, and the sentence *The experience in treating women older than 65 years is limited* was removed, as it is considered outdated.

The applicant has submitted a clinical trial which demonstrates therapeutic equivalence between Vagidonna (Test) and Vagifem (Reference). In this trial, 442 postmenopausal women with vaginal atrophy were randomised to 2 weeks of daily administration of 10 microgram estradiol vaginal tablet (Test; n=203) or Vagifem (Reference; n=179) or Placebo (n=60) followed by 4 weeks of biweekly administration of the same. 415 completed the clinical trial according to the protocol, 27 subjects dropped out during the study. The placebo group was discontinued after 2 weeks.

The subjects enrolled in the study were postmenopausal women, mean age about 59 years. The participants were all Caucasian. Medical history was similar between groups, as were baseline data regarding age, body weight, BMI, height and smoking habits. Laboratory values and vital signs were also similar. The subjects included are deemed to be representative of the vaginal atrophy population, although inclusion of women at a slightly higher age would have been an advantage.

The study was performed in 3 different European countries, with a majority of patients recruited in Bulgaria. The PK part of the study was performed in one site in Germany. Neither the number of patients with vaginal atrophy nor the treatment results are expected to vary greatly between European countries.

As each of the active treatments was delivered using its own applicator, a double-dummy approach was used in order to achieve double blind conditions. For this purpose, each active treatment was administered with its own applicator together with an additional placebo tablet applied with the applicator device of the other active treatment. Thus, each patient received two vaginal tablets per administration.

Two primary endpoints were used: change from baseline in vaginal maturation value (MV) after 2 weeks treatment and change from baseline of vaginal pH after 6 weeks of treatment. These are readily measured outcomes for oestrogen effect on the vaginal wall and are in line with scientific advice given to the Applicant. There are several ways to calculate MV described in the published literature. The Applicant has justified the preference of MV1 over other available methods for describing and calculating maturation of the vaginal epithelium.

Change from baseline of signs (investigator's assessment) and symptoms (subject's self-assessment) of vaginal atrophy evaluated descriptively are used as secondary efficacy parameters. The chosen secondary parameters, though less objective, are deemed to contribute clinically relevant information.

The sample size was planned in an adaptive two-stage design with an interim analysis after stage I. The sample size was driven by the test for equivalence between Test and Reference. After the first stage was analysed, the sample size was set to 430 subjects and the placebo arm was omitted and the allocation ratio for the study population was 1:1 throughout the study.

The tablets themselves, Test vs Reference, are described as visually similar, thus not identical. The applicators are visibly diverse. The main problem of blinding is in relation to the applicators, rather than the tablets themselves. Blinding is achieved as all patients have received visually identical treatment: one tablet of Reference or placebo for Reference delivered in the applicator of Reference, and one tablet of Test or placebo for Test delivered in the applicator for Test.

The primary analysis was based on the modified FAS which excluded subjects who did not receive any treatment or did not fulfil all major entry criteria or did not provide at least one data value necessary post-baseline for the primary endpoints. Hence, this analysis set is not according to the ITT principle but a per protocol analysis. The Applicant has, however, also presented an analysis according to the ITT principle where all subjects are included. This analysis is consistent with previously presented results and hence supports the conclusions.

For primary variables, missing data were imputed with a multiple imputation method. This method assumes that data are missing at random (MAR). Three sensitivity analyses were presented, none of which is considered to challenge the MAR assumption. The Applicant has presented sensitivity analyses which do not rely on the MAR assumption. These analyses support the conclusions.

Superiority versus placebo as well as equivalence versus Reference were to be demonstrated for both primary variables. Hence it is agreed that no adjustment for multiple testing was needed (except for the interim analysis). The primary analysis was based on multiple imputation with the method specified in the SAP.

The equivalence margins for MV and vaginal pH was chosen at 6.5 and 0.4 respectively, based on a literature survey which identified a total of 3 publications, where thresholds of clinical significance were applied for the comparison of two active treatments. The averages from those publications were 6.7 and 0.5 for MV and vaginal pH, respectively. In addition, a statistical approach was applied in order to support the choice of equivalence margins. The effect of the reference treatment versus placebo was estimated by the lower boundary of the two-sided 95 % confidence interval obtained from a meta-analysis including placebo controlled clinical trials found in the literature. Then, 50 % of this amount was taken as equivalence margin. The Applicant identified 6 and 3 relevant publications which led to equivalence margins of 6.5 and 0.4 for MV and vaginal pH respectively, which also were the margins chosen by the Applicant.

For both primary parameters, MV as well as vaginal pH, results suggest improved maturation status of the vaginal mucosa for Test and Reference, similar for both groups, and significantly less improvement in the placebo group. MV in both treatment groups increased from 40 % MV to 60 % MV (arithmetic means) within 2 weeks of treatment. Vaginal pH in both treatment groups decreased from 6.5 to 5.0 vaginal pH (arithmetic means) within 6 weeks of treatment. The results suggest therapeutic equivalence between Test and Reference

Symptoms of vaginal atrophy as assessed by the subjects themselves, also revealed comparable treatment effects in Test and Reference. The observed effects of placebo treatment were slightly smaller than those observed under active treatment.

The method of subject’s self-assessment of treatment effects via questionnaires is highly subjective, and the difference between placebo and active treatment was less pronounced than in the results of the more objective measurements.

Results for the secondary parameters support the equivalence between groups. These results also suggest superiority over placebo, but less markedly so.

Thus, it is concluded that therapeutic equivalence between Vagidonna and Vagifem was shown regarding the primary, readily assessed parameters maturation of the epithelial mucosa (MV) and vaginal pH, as well as for the more subjective, less easily evaluated, but clinically relevant secondary parameters measuring change from baseline of signs (investigator’s assessment) and symptoms (subject’s self-assessment) of vaginal atrophy evaluated descriptively.

IV.5 Clinical safety

Low dose oestrogen for vaginal administration has been used extensively in the treatment of vaginal atrophy for many years. The safety of 10 microgram estradiol delivered vaginally is considered well established.

Safety evaluations in the clinical trial were performed for all subjects randomised into the trial who received at least one dose of treatment (442 subjects; 203 Test, 179 Reference and 60 Placebo) in the PD group and the PK group (27 subjects; 13 Test and 14 Reference).

The total drug exposure within the PD group of this trial according to the protocol was 220 µg of estradiol resulting from treatment of 14 days with 10 µg of estradiol per 24 h during the

initial treatment period, followed by 4 weeks maintenance period with 2 x 10 µg of estradiol per week. In 356 out of 382 subjects (PD excluding placebo group) the drug application was performed strictly in accordance with the protocol during the initial treatment phase. For the maintenance period, drug application in accordance with the protocol was confirmed for 349 out of 361 subjects, excluding drop-outs and placebo group.

The PK group of this trial only completed the 14 treatment days of daily applications, resulting in 140 µg of estradiol (14 days with 10 µg of estradiol per 24 h). This level of exposure was confirmed for 23 out of 27 subjects.

In general, there were no apparent differences between the Test and the Reference in any of the parameters examined: vital signs, local tolerability, transvaginal ultrasonography, adverse events or clinical laboratory and cervical smear tests.

With regard to adverse events, there does not appear to be any difference in frequency or type or severity between treatments (Test or Reference). The events described are not unexpected to occur in the particular population under study.

The incidence of serious AEs was generally low and none of the observed cases was related to study drug intake. No clinically relevant changes in vital signs or laboratory findings were noted.

In seven patients, endometrial thickness >5mm was found on vaginal ultrasound. In half of the patients, the thickness resolved during follow-up. Considering the short treatment period and the low systemic exposure to estradiol, the findings are unlikely to be associated with the treatment.

For safety reasons, a PK study was performed to demonstrate that the vaginal administration of 10 microgram estradiol does not result in significant systemic uptake of estradiol. The plasma concentration vs. time curves and the calculated PK parameters at the end of the 14-day initial treatment phase suggest that the systemic exposure with estradiol under both treatments remains low and that the exposure from Test was not higher to that of Reference.

In clinical practice, low dose vaginal oestrogen is regularly used for considerably longer time periods than what is currently common for systemic hormone replacement therapy. There is thus a considerable number of elderly women treated for long periods of time, sometimes lifelong. In this respect, the lack of studies demonstrating efficacy and safety in women older than 65 for Vagidonna, as well as for the reference product, is a concern.

The applicant has made a subgroup analysis in women <65 and > 65 years in the provided study and found no difference. The small population of the age group >65 years, less than 20% of the total population, does not allow comprehensive statistical evaluation. However, it can be deduced that for the age group > 65 years, effects are similar to those in the total population investigated in this trial. The outcome supports the assumption that there is no difference in efficacy and safety in the population >65 years. This is in line with clinical experience and the lack of reports of higher incidence of adverse events in older patients.

The very low systemic exposure from low dose oestrogen administered through the vaginal route is an advantage in elderly women, posing few, if any, apparent risks. Considering that women >65 years are a principal target population for treatment, and that there is little safety concern even in the elderly population, the sentence “The experience in treating women older than 65 years is limited” from 4.1 of the SmPC is removed.

Risk Management Plans

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 Vagidonna. The table of safety specification lists a number of risks that are listed in the SmPC. These are well characterised and are not considered to need additional follow-up.

Safety specification

Important identified risks	None
Important potential risks	None
Missing information	None

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

Risk minimisation measures

Routine risk minimisation is suggested and no additional risk minimisation activities are proposed by the applicant.

Summary of the RMP

The submitted Risk Management Plan was accepted in Day 180 RMS response AR. The MAH was changed late in the procedure and unfortunately there was a mistake in the RMP v1 dated 13 February 2020. A corrected RMP v1.1 dated 20 March 2020 was received.

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the RMS;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time, but via different procedures.

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 Spanish.
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

The benefit/risk ratio is considered positive and Vagidonna, Vaginal tablet, 10 µg, is recommended for approval.

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

N/A

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

N/A

VII. APPROVAL

The decentralised procedure for Vagidonna, Vaginal tablet, 10 µg was positively finalised on 2020-03-15.

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SWEDISH MEDICAL PRODUCTS AGENCY

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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