



HUNGARIAN NATIONAL CENTER FOR PUBLIC HEALTH AND PHARMACY

Public Assessment Report

Scientific discussion

Vagirux 10 mikrogramm hüvelytabletta
(estradiol hemihydrate)

HU/H/0632/001/DC

Date: 20.05.2026.

This module reflects the scientific discussion for the approval of Vagirux 0,01 mg vaginal tablets. The procedure was finalised at 02. 07. 2020. For information on changes after this date please refer to the module 'Update'.

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted marketing authorisation for Vagirux 0,01 mg vaginal tablets.

The active substance is estradiol hemihydrate, in a vaginal tablet that has been developed for treatment of vaginal atrophy in postmenopausal women.

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

The originator product is Vagifem 10 micrograms vaginal tablets by Novo Nordisk A/S, registered since 12-02-2010.

Since estradiol-containing vaginal tablets are considered as “locally applied, locally acting” drug products, demonstration of therapeutic equivalence instead of pharmacokinetic bioequivalence is required according to applicable European guidance (CPMP/EWP/239/95).

To show the therapeutic equivalence between test and reference formulations, a clinical study has been conducted.

II. QUALITY ASPECTS

1. Introduction

The chemical-pharmaceutical assessment report concerns the application of Vagirux 10 microgram vaginal tablets via a decentralized procedure according to Article 10.3 of Directive 2001/83/EC (i.e a hybrid application). The products have been developed by Helm.

Reference product is Vagifem® vaginal tablet (containing 10 microgram estradiol as active ingredient) which were the original products of Novo Nordisk A/S.

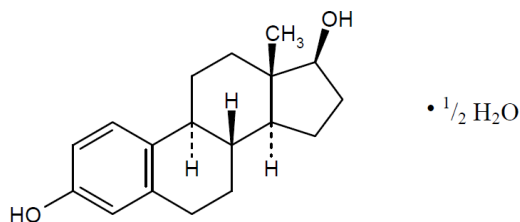
2. Drug Substance

Data on the quality and manufacture of the active substance were provided in the applicant's submission using the CEP procedure with additional data in the marketing authorization dossier. The Quality Overall Summary is adequate.

INN name: Estradiol hemihydrate

Chemical name: (17 β)-estra-1,3,5(10)-triene-3,17-diol; (17 β)-estra-1,3,5(10)-triene-3,17-diol hemihydrate

Structure:



The active substance is white or off-white crystalline powder or colourless crystals, practically insoluble in water, soluble in acetone, sparingly soluble in ethanol (96 per cent), slightly soluble in methylene chloride. It shows polymorphism, the manufacturer consistently produces the correct isomer and the same polymorphic form.

The substance is specified according to the requirements of the current Ph.Eur. monograph, additional specification has only been set for residual solvent and particle size distribution. The presented specification is in accordance with the Ph.Eur. general monograph on *Substances for Pharmaceutical Use* and the ICH Q6A guideline. The specifications reflect all relevant quality attributes of the active substance and were found to be adequate to control the quality of the drug substance. The limits set are properly justified.

Testing methods not described in details in the Pharmacopoeia are adequately drawn up and sufficiently validated. Reference materials used by the active substance manufacturer and the drug product manufacturer for the control of the substance are adequately characterised. The substance complies with the requirements of the EMA guideline on genotoxic impurities.

Batch analysis data justify the limits, indicate the good performance of testing methods and demonstrate the batch to batch consistency of the production.

A retest period and the packaging material have been mentioned on the CEPs.

Good Manufacturing Practice (GMP) compliance of the API manufacture is demonstrated by the applicant.

3. Medicinal Product

The aim was to develop vaginal tablets containing estradiol hemihydrate as drug substance in 10 microgram doses pharmaceutically equivalent to the reference medicinal product Vagifem® vaginal tablet, the branded original products of NovoNordisk.

A satisfactory package of data on development pharmaceuticals has been presented. Brief discussion on reasons for inclusion and quantity of excipients has been provided.

As regards dissolution and impurity profile the product is shown to be similar to the reference product.

The compositions and the pharmaceutical tests evaluated during development of the final formulation are included in the documentation. As a result of development studies product with the following appearance and composition was obtained.

Vagirux 10 microgram vaginal tablets are white, round, film coated tablet embossed with "E" one side and plain on the other side. The tablets have a diameter of about 6 mm.

The excipients used in the finished product are hypromellose, lactose monohydrate, maize starch, magnesium stearate and film-coating (macrogol and hypromellose). All excipients used comply with their respective European Pharmacopoeia monograph. Compliance of the product with the general monograph of the European Pharmacopoeia *on the Products with the risk of TSE* has been demonstrated by the applicant.

A description and flow chart of the manufacturing method has been provided. Appropriate in-process controls are included in the manufacturing process. Satisfactory batch formulae were also presented. GMP compliance of the manufacturing site has been demonstrated.

The finished product specification is satisfactory. Acceptance criteria have been justified with respect to conventional pharmaceutical requirements as prescribed in the relevant dosage form monograph of the Ph.Eur. and the ICH Q6A guideline. Appropriate control strategy was selected. The test methods have been described and have been adequately validated, as appropriate. Batch data have been provided and complied with the specification.

The container closure system of the product is PVC/PVdC//Al blister. The blisters are packed into cardboard boxes accompanied by applicators separately sealed in foil. Specifications and quality certificates for all packaging components are enclosed.

Finished product stability studies have been conducted in accordance with the current guidelines. Based on the results, a **shelf-life of 2 years** is approved with the following storage restriction: “Keep the blisters in the outer carton in order to protect from light”.

The Summary of Product Characteristics, patient Information Leaflet and label texts are pharmaceutically acceptable.

4. Discussion on chemical, pharmaceutical and biological aspects

Conclusion: The product has been shown to meet the current regulatory requirements with regards to its quality and content of the active substance as well as dosage-form characteristics until the end of the approved shelf-life consistently. The manufacture and the quality standards applied adequately support the safe use and efficacy of the product.

III. NON-CLINICAL ASPECTS

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

The submitted non-clinical overview on the non-clinical pharmacology, pharmacokinetics and toxicology of Vagirux is considered adequate.

1. Environmental risk assessment (ERA)

The product is intended as a substitute for the originator product on the market. The approval of this product will not result in an increase in the total quantity of estradiol hemihydrate released into the environment. An environmental risk assessment is therefore not deemed necessary.

2. Discussion on the non-clinical aspects

Pharmacodynamics, pharmacokinetics and toxicology of estradiol hemihydrate are well-known. There are no objections to the approval of these applications from a non-clinical point of view.

IV. CLINICAL ASPECTS

1. Introduction

Vagirux (estradiol hemihydrate 10 µg vaginal tablets) are low dose intravaginal hormone replacement therapy containing 17β-estradiol.

The estrogen component 17β-estradiol is identical to endogenous human estradiol. 17β-estradiol compensates for the reduced levels of estrogens in postmenopausal women and among other symptoms, reduces the vaginal atrophy related to estrogen deficiency. Intravaginally administered low-dose estradiol vaginal tablets are effective for the relief of vaginal atrophy symptoms.

Vagirux 0,01 mg vaginal tablets were designed to deliver a lower dose of 17β-estradiol directly to the vaginal tissues with minimal systemic absorption.

The clinical pharmacodynamics, pharmacokinetics, efficacy and safety of the active ingredient in the proposed indications, doses and dosing regimens are well known.

The proposed indications are:

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

For the detailed approved indications and recommended dose see the Summary of Product Characteristics.

2. Pharmacokinetics

Absorption

The absorption of estradiol in humans has been studied extensively; however, the results are difficult to compare as different preparations of estradiol and different routes of administration have been used. In a pharmacokinetic study it was concluded that treatment with 25 or 10 µg of 17 β-E2 vaginal tablets resulted in low absorption of estrogen without systemic effects often associated with hormone replacement therapy. After 12 weeks of therapy for atrophic vaginitis, absorption patterns remained consistent, and women did not have accumulations of circulating E2.

The average E2 concentrations at each time point were within the normal postmenopausal range.

Distribution and protein binding

Estrogens circulate in the blood bound to albumin (ca 60%), sex hormone-binding globulin (SHBG), α1-glycoproteins and transcortin.

The production of SHBG is stimulated by increasing estrogen concentrations. Because of the high concentration of albumin (approximately five orders of magnitude higher than SHBG) and the rapid dissociation, albumin may serve a more important regulating role than SHBG.

The distribution volume of E2 is small (about 70 l), and approximates 1.5-2 times of the total body water in fertile women.

Metabolism

The metabolic disposition of estrogens includes oxidative metabolism (largely hydroxylation) and conjugative metabolism by glucuronidation, sulfonation and/or methylation. Estradiol is converted to estrone by a 17β-hydroxysteroid dehydrogenase; the estrone produced is further metabolized to 16α-hydroxyestrone and then to estriol. Estrone sulphate constitutes the largest pool of estrogen in the body and serves as a reservoir primarily for estrone.

Elimination

Estrone is not tightly bound to plasma proteins and therefore has a higher clearance rate than estradiol. Estrone sulfate is quantitatively the most important plasma estrogen metabolite and is bound with high affinity to albumin, 90% circulating in bound form. Estrone sulfate is considered to have a large, slowly metabolized reservoir, with 90% of its mass bound to albumin; accordingly, it has a low metabolic clearance rate (about 150 L/24 h) and low renal clearance.

3. Pharmacokinetic study

In the therapeutic equivalence study systemic exposure was assessed in a separate PK group with 28 volunteers, which ran through PK characterisation only. The objective of the study was to establish that the plasma exposure of the Test product was not higher than for the Reference. The study has been conducted following 14 days of daily administration of the investigational products (parallel design), hence steady-state concentrations have been evaluated.

Baseline corrected individual plasma concentration vs. time curves for Test and Reference increase up to about 10 pg/ml above the endogenous estradiol baseline. During the 24 h-profiling most subjects presented a moderately fluctuating plateau and about 9 subjects exhibited an increase with subsequent decrease indicating a pharmacokinetic absorption and distribution / elimination phase. However, for none of the subjects a significant increase in exposure was observed.

The data and individual curves present a high inter-individual variability. Nevertheless, systemic absorption in all patients was generally low and very similar for both treatments. The time point of reaching maximum exposure, represented by median values of $t_{max,ss}$, is slightly earlier for Test (10.00 h) than for Reference (12.00 h).

Maximum observed estradiol concentrations (without baseline correction) remained below 20 pg/ml in all subjects under Test as well as Reference treatment. The highest individual $C_{max,ss}$ under Test treatment was 18.06 pg/ml, under Reference treatment this was 18.58 pg/ml.

After further requested calculation, the point estimates were below 100%, and the upper limit of the 90% confidence intervals were also below the usual bioequivalence limit of 125.00%, hence it can be concluded that the systemic exposure for the Test product is not higher than for the Reference product.

4. Pharmacodynamics

The drug product contains active substance estradiol hemihydrate..

Estradiol and its semisynthetic esters and other natural oestrogens are mainly used as menopausal hormone replacement therapy (HRT). Estradiol (oestradiol, 17 β -estradiol) is the most active of the naturally occurring oestrogens.

The established benefits of estrogen therapy in postmenopausal women include amelioration of vasomotor symptoms and the prevention of bone fractures and vaginal atrophy. 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.

17 β -estradiol compensates for the reduced levels of estrogens in postmenopausal women and reduces the vaginal atrophy related to estrogen deficiency.

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.

Intravaginally administered low-dose estradiol vaginal tablets are effective for the relief of vaginal atrophy symptoms and are safer than oral tablets, due to low systemic exposure.

5. Clinical efficacy

Although postmenopausal atrophic vaginitis is a common condition in elderly women, only a small percentage of those affected receive treatment with estrogens. In symptomatic women who have no other indications for systemic hormone replacement or prefer not to use systemic therapy, local vaginal treatment with estrogen is effective in reversing atrophic vaginal changes and relieving symptoms.

Previously vaginal tablets contained 25 μ g estradiol were used. Since ultra-low dose 10 μ g tablets have shown similar efficacy, this is now the most widely used dose.

To show the therapeutic equivalence between Vagirux and the reference Vagifem 10 μ g vaginal tablets, a clinical study (HELM Study No.: 148-2016) has been conducted.

This was a multi-centre, multi-national, double-blind, double-dummy randomised (allocation of treatments), balanced, multiple-dose clinical trial performed following a parallel-group design with active and placebo control in postmenopausal female subjects with vaginal atrophy.

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 study was performed in Bulgaria, Moldova and Germany.

The trial intended to assess the pharmacodynamic (PD) effect upon vaginal maturation value (MV) and vaginal pH in the pharmacodynamic part as primary efficacy assessment. The two primary endpoints were: change from baseline in MV after 2 weeks treatment and change from baseline of vaginal pH after 6 weeks of treatment.

As secondary efficacy parameters the changes in signs and symptoms of vaginal atrophy were assessed.

In addition, systemic exposure was assessed in a separate PK group, which ran through PK characterisation only.

In general safety evaluations for this trial have been performed for all subjects who were randomised into the trial and received at least one dose of treatment in the PD group and also in the PK group.

Overall, the study design is considered acceptable .

The vaginal maturation value and vaginal pH are commonly used parameters for objectively assessing efficacy of a medication in improving or reverting vaginal atrophy.

Based on the literature data the formula MV1 appears to be adequate for assessing the maturation of vaginal mucosa, and for comparing the efficacy of the two products.

Changes from baseline in signs and symptoms of vaginal atrophy are more subjective parameters than MV or vaginal pH, however adequate as supportive parameters.

Primary and secondary endpoints are suitable to demonstrate therapeutic equivalence of the two products.

The objectives and primary/secondary endpoints are acceptable.

The studied population is representative for the intended target population.

Signs and symptoms of vaginal atrophy are adequately covered by the inclusion criteria.

The exclusion criteria meet the requirements for the use of the product.

The dose was chosen according to the posology recommended in the SmPC of the reference product Vagifem 10 µg vaginal tablets.

An adaptive two-stage design was chosen for the study, since limited amount of data was available on the treatment effect and variability for the endpoints, and the sample size calculations were uncertain. The trial was continued after the interim analysis with modified design, increased sample size and placebo arm was omitted.

According to the submitted literature data the clinical study-based threshold for equivalence margins were 6,67 for MV and 0,5 for pH.

In addition, based on the further statistical consideration the margins were chosen as of 6.5 and 0.4 for MV and vaginal pH.

Based on the results of the clinical trial the superiority of the investigated Test and Reference compared to the Placebo regarding to the chosen vaginal maturation value was shown.

MV in both test and reference groups increased similarly (from 40 % MV to 60 % MV (arithmetic means) within the initial two weeks of treatment.

Vaginal pH decreased from 6.5 to 5.0 pH value (arithmetic means) within 6 weeks of vaginal estradiol treatment in both test and reference groups, indicating the improving atrophic status of the vaginal mucosa under treatment.

Statistical methods used in the assessment of the study seem adequate.

Although changes from baseline in signs and symptoms of vaginal atrophy assessed by the investigator, or mainly the (self)assessed by the subjects are more subjective parameters than the

objective measurements for the surrogate parameters MV and vaginal pH, the results demonstrated similarly greater treatment effect under Test and Reference than under Placebo treatment. These are adequate supportive parameters in comparison of the efficacy of the test and reference products.

6. Clinical safety

Low dose estradiol products for vaginal administration has been widely used for many years in the treatment of vaginal atrophy.

The 10 microgram estradiol delivered vaginally is considered well established and the published data support the safety of ultra low-dose local estrogen therapies.

Vagirux 10 µg tablets were designed to deliver a lower dose of 17β-estradiol directly to the vaginal tissues with minimal systemic absorption.

Due to low systemic exposure Vagirux is considered to be safer than oral tablets.

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

With regard to adverse events, there did not appear to be any difference in frequency or type or severity between treatments (Test or Reference).

The TEAEs experienced during the study were mainly mild or moderate in intensity.

Side effects reported are well known side effects of estrogen therapy and vaginal administration.

The description of the serious adverse events was adequately detailed. The incidence of SAEs 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.

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

For safety reasons, a PK study was performed to evaluate that the vaginal administration of 10 microgram estradiol does not result in significant systemic uptake of estradiol, and it has been demonstrated that the systemic exposure is comparable to that of the reference, and does not exceed the physiological range of estradiol known in the postmenopausal state.

7. Discussion on the clinical aspects

The application contains an adequate review of published clinical data.

Based on the data of the therapeutic equivalence study it is concluded that therapeutic equivalence between Vagirux 0,01 mg vaginal tablets 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.

The TEAEs experienced during the study were mainly mild or moderate in intensity.

Side effects reported are well known side effects of estrogen therapy and vaginal administration.

For safety reasons, a PK study was performed to evaluate that the vaginal administration of 10 microgram estradiol does not result in significant systemic uptake of estradiol, and it has been demonstrated that the systemic exposure is comparable to that of the reference, and does not exceed the physiological range of estradiol known in the postmenopausal state.

Thus approval is recommended from the clinical point of view.

8. Pharmacovigilance

Vagirux 10 mikrogramm hüvelytabletta

Applicant: Richter Gedeon Vegyészeti Gyár Nyrt.

Active substance: Estradiol hemihydrate;

HU/H/0632/001/DC, OGYÉI/26408/2019

Summary of Pharmacovigilance System

The Applicant has submitted a signed Summary of the Applicant's Pharmacovigilance System. Provided that the Pharmacovigilance System Master File fully complies with the new legal requirements as set out in the Commission Implementing Regulation 520/2012 and as detailed in the relevant GVP module, the Summary is considered acceptable.

Risk Management Plan

- **Summary of safety concerns**

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

As the active substance (estradiol hemihydrate) has been used for decades and its safety concerns are well-known so there were no safety concerns applicable for this EU RMP based on the requirement to present only the important identified or potential risks and missing information linked to further pharmacovigilance activities or additional risk minimization measures in the EU.

- **Pharmacovigilance Plan**

Routine pharmacovigilance activities are considered sufficient to manage all of the safety concerns connected to Richter's product containing estradiol hemihydrate.

No additional activities are proposed.

- **Risk Minimisation Measures**

Routine risk minimisation measures (i.e. wording in SmPC, PL and classification as a prescription only medicine) are considered sufficient to manage all of the safety concerns connected to Richter's product containing estradiol hemihydrate.

No additional activities are proposed. For any further information on risk minimisation, please refer to the product information.

PSUR

The requirements for submission of periodic safety update reports for these medicinal products are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

V. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The present application concerns Vagirux 0,01 mg vaginal tablets.
The applicant and the future holder of authorisation is Gedeon Richter Plc.

The application was submitted according to Article 10(3) of Directive 2001/83/EC (hybrid application). The originator product is Vagifem 10 micrograms vaginal tablets by Novo Nordisk A/S, registered since 12-02-2010.

The product is indicated for the treatment of vaginal atrophy due to estrogen deficiency in postmenopausal women.

The submitted documentation is administratively adequate and scientifically sound. The quality of the product is satisfactory. There were no non-clinical or clinical concerns raised.

The therapeutic benefit/risk assessment is therefore positive.

Based on the review of the quality, safety and efficacy data, the Member States have granted marketing authorisation for Vagirux 0,01 mg vaginal tablets.

Modul 6

Steps taken after the initial procedure with an influence on the Public Assessment Report

Procedure number	Type of modification ¹	Date of start of the procedure	Date of end of procedure	Approval/non approval
HU/H/0632/1/IA/001	C.I.z). Other variation to implement the EMA/PRAC/257435/2020	2020.08.29	2020.09.29	Positive
HU/H/0632/1/IA/002	B.IV.1.a).1. Device with CE marking	2021.07.28	2021.08.27	Positive
HU/H/0632/1/IB/003	C.I.z). Other variation	2022.03.16	2022.04.15	Approved
HU/H/0632/1/II/004	B.II.d).1.e). Change outside the approved specifications limits range	2024.01.30	2024.03.30	Approved