COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Estradiol/Drospirenon Gedeon Richter 1 mg/2 mg film-coated tablets

(estradiol hemihydrate/drospirenone)

NL/H/4588/001/DC

Date: 12 November 2019

This module reflects the scientific discussion for the approval of Estradiol/Drospirenon Gedeon Richter 1 mg/2 mg. The procedure was finalised on 20 September 2019. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CMS	Concerned Member State
EDQM	European Directorate for the Quality of Medicines
EEA	European Economic Area
ERA	Environmental Risk Assessment
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
NLT	Not Less Than
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
RH	Relative Humidity
RMP	Risk Management Plan
SmPC	Summary of Product Characteristics
TSE	Transmissible Spongiform Encephalopathy

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Estradiol/Drospirenon Gedeon Richter 1 mg/2 mg film-coated tablets from Gedeon Richter Plc.

The product is indicated for

- Hormone replacement therapy for estrogen deficiency symptoms in postmenopausal women more than 1 year post menopause.
- Prevention of osteoporosis in postmenopausal women at high risk of future fractures who are intolerant of, or contraindicated for, other medicinal products approved for the prevention of osteoporosis. (see also section 4.4 of the approved SmPC)

The experience treating women older than 65 years is limited.

A comprehensive description of the indications and posology is given in the SmPC.

This decentralised procedure concerns a generic application claiming essential similarity with the innovator product Angeliq 1 mg/2 mg film-coated tablets (NL Licence RVG 27505) which has been registered in the Netherlands by Bayer B.V. since 11 December 2002 (MRP NL/H/0380/001).

The concerned member states (CMS) involved in this procedure were Belgium, Czech Republic, Finland, France, Germany, Italy, Latvia, Poland, Portugal, Spain and the United Kingdom.

The marketing authorisation has been granted pursuant to Article 10(1) of Directive 2001/83/EC.

II. QUALITY ASPECTS

II.1 Introduction

Estradiol/Drospirenon Gedeon Richter 1 mg/2 mg is a white or almost white, round, biconvex film-coated tablet, engraved on one side with 'GD3', other side is without engraving.

Each film-coated tablet contains 1 mg estradiol (as 1.03 mg estradiol hemihydrate) and 2 mg drospirenone.

The film-coated tablets are packed in transparent PVC/PVDC//Al blister in carton box with a patient information leaflet, and etui storage bag, enclosed in each box.

The excipients are:
Film-coating - polyvinyl alcohol, titanium dioxide (E 171), macrogol 3350, talc, lecithin (soya)
Tablet core - lactose monohydrate, maize starch, pregelatinized starch (maize), povidone K-25, magnesium stearate

II.2 Drug Substances

Drospirenone
The first active substance is drospirenone, an established active substance described in European Pharmacopoeia (Ph.Eur.) The active substance is a crystalline powder and is practically insoluble in water. his active substance does not exhibit polymorphism, and particle size is not relevant due to the fact that the active substance is added in dissolved form during granulation.

The CEP procedure is used for the active substance drospirenone. Under the official Certification Procedures of the EDQM of the Council of Europe, manufacturers or suppliers of substances for pharmaceutical use can apply for a certificate of suitability concerning the control of the chemical purity and microbiological quality of their substance according to the corresponding specific monograph, or the evaluation of reduction of Transmissible Spongiform Encephalopathy (TSE) risk, according to the general monograph, or both. This procedure is meant to ensure that the quality of substances is guaranteed and that these substances comply with the Ph.Eur.

Manufacturing process
A CEP has been submitted; therefore no details on the manufacturing process have been included.

Quality control of drug substance
The active substance specification is in line with the Ph. Eur. The specification is acceptable in view of the route of synthesis and the various European guidelines. Batch analytical data demonstrating compliance with the drug substance specification have been provided for three commercial batches.

Stability of drug substance
The active substance is stable for 48 months when stored under the stated conditions. Assessment thereof was part of granting the CEP and has been granted by the EDQM.

Estradiol
The other active substance is estradiol hemihydrate, an established active substance described in the European Pharmacopeia. The active substance is a crystalline powder or colourless crystals and is practically insoluble in water.

This active substance does not exhibit polymorphism. The MAH has specified that micronized estradiol hemihydrate is used in this drug product. The CEP procedure is used.

Manufacturing process

A CEP has been submitted; therefore no details on the manufacturing process have been included.

Quality control of drug substance

The active substance specification is in line with the Ph. Eur except for the additional requirements for particle size distribution which is given as "in-house". The specification is acceptable in view of the route of synthesis and the various European guidelines.

Batch analytical data demonstrating compliance with the drug substance specification have been provided for three commercial batches.

Stability of drug substance

The active substance is stable for 5 years when stored in double polyethylene bags placed in fibre drums. This aspect has been evaluated within the scope of the CEP procedure by the EDQM and the conclusion is taken from the CEP.

Stability data on the active substance has been provided by the MAH for the micronized active substance estradiol hemihydrate micronized active substance, which is not covered by the CEP.

Long-term stability studies have been given for seven commercial size batches from samples stored in the marketing packaging which is that stated in the CEP for up to 60 months for at least three of the batches. The conditions used were 25±2°C, 60±5 %RH, protected from light.

On the basis of the available data obtained with estradiol hemihydrate micronized, the MAH has concluded that particle size distribution of estradiol hemihydrate micronized meets the acceptance criteria up to 60 months and that the test results also confirm that the impurity levels of specified, unspecified, other and total impurities are also within specification limits within the testing periods.

Based on the data provided the proposed retest period of up to 60 months and storage condition are justified.

II.3 Medicinal Product

Pharmaceutical development

The development of the product has been described, the choice of excipients is justified and their functions explained. The excipients chosen are the same as those of the reference product so compatibility studies of the active substances were considered unnecessary. The MAH has discussed functional related characteristics for relevant excipients adequately. The pharmaceutical development of the product has been adequately performed.

The MAH has performed a bioequivalence study and has provided complementary dissolution data of the batches used in the BE study, in four media (QC, 0.001 M HCl, pH 4.5 and pH 6.8). The dissolution profiles of the batches are similar in all conditions, either by having > 85% active substances dissolved in 15 min or by showing acceptable f2 values.

The manufacturing process development has been described in sufficient detail, with results of lab-scale and scaled-up batches provided and critical process parameters discussed.

Manufacturing process

The (non-standard) manufacturing process consists of wet granulation with drospirenone dissolved in ethanol and estradiol in the intragranulary mixture, drying and sizing of the granules, lubrication, compression and film-coating. The process has been described in detail. The in-process controls have been described in sufficient detail and the limits are acceptable. The manufacturing process has been adequately validated according to relevant European guidelines. Process validation data on the product has been presented for three full-scale batches.

Control of excipients

The excipients comply with Ph. Eur and in-house requirements as relevant. The MAH has provided certificates of analysis for all of the excipients instead of specifications. Acceptance criteria, tests and analytical methods have been included for each of the excipients.

Quality control of drug product

The product specification includes tests for characters, identification, uniformity of mass, uniformity of dosage units, related substances, microbiological purity, ethanol, assay and dissolution. The release and shelf-life specification are identical except for the limits of related substances (specified and total). The limits for specified and total impurities at end of shelf-life have been adequately tightened, based on stability data. The limit for dissolution for drospirenone has been tightened to NLT 85% (Q) in 15 min as requested based on the dissolution profile of the BE batch. The MAH has justified the choice of the dissolution limit of NLT 80% (Q) in 30 min for estradiol, which has been accepted. The analytical methods have been adequately described. The in-house analytical procedures for assay, related substances, ethanol, dissolution, microbial purity and stability indicating nature have been adequately validated. Batch analytical data from the proposed production site have been provided on three full-scale batches, demonstrating compliance with the proposed release specification.

Stability of drug product

Stability data on the product has been provided three full-scale batches stored at 30°C ± 2°C/65% RH ± 5% RH and accelerated stability studies at 40°C ± 2°C/75% RH ± 5% RH . The conditions used in the stability studies are according to the ICH stability guideline. The batches were stored in PVC/PVDC//Alu blister + carton box. Photostability studies were performed in accordance with ICH recommendations and showed that the product is stable when exposed to light.

In view of the tightening of the dissolution limit, and the confirmation/submission of the stability data at the tightened limit, a shelf life of 24 months has been granted. The proposed medicinal product does not require any special storage conditions.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
There are no substances of ruminant animal origin other than lactose monohydrate present in the product. Risk of transmitting TSE can be excluded based on TSE/BSE statements.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Estradiol/Drospirenon Gedeon Richter 1 mg/2 mg film-coated tablets has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substances and finished product. No post-approval commitments were made.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Estradiol/Drospirenon Gedeon Richter is intended for generic substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

III.2 Discussion on the non-clinical aspects

This product is a generic formulation of Angeliq, which is available on the European market. Reference is made to the preclinical data obtained with the innovator product. A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is based on up-to-date and adequate scientific literature. The overview justifies why there is no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data. Therefore, the member states agreed that no further non-clinical studies are required.

IV. CLINICAL ASPECTS

IV.1 Introduction

Estradiol hemihydrate and drospirenone are well-known active substances with established efficacy and tolerability. A clinical overview has been provided, which is based on scientific literature. The overview justifies why there is no need to generate additional clinical data. Therefore, the member states agreed that no further clinical studies are required.

For this generic application, the MAH has submitted a bioequivalence study, which is discussed below.

IV.2 Pharmacokinetics

The MAH conducted a bioequivalence study in which the pharmacokinetic profile of the test product Estradiol/Drospirenon Gedeon Richter 1 mg/2 mg (Gedeon Richter Plc., Hungary) is compared with the pharmacokinetic profile of the reference product Angeliq 1 mg/2 mg film-coated tablets (Bayer Pharma AG, Germany).

The choice of the reference product in the bioequivalence study has been justified by comparison of dissolution results and compositions of reference products in different member states. The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

Bioequivalence studies

Design

A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in twenty-eight healthy post-menopausal women, aged 43 - 65 years. Each subject received a single dose (1 mg/2 mg) of one of the 2 estradiol/drospirenone formulations. The tablet was orally administered with 240 ml water after an overnight fast. There were 2 dosing periods, separated by a washout period of 28 days.

Blood samples were collected pre-dose and at 0.25, 0.5, 0.75, 1, 1.25, 1.5, 1.75, 2, 3, 4, 5, 6, 7, 8, 10, 12, 16, 24, 36, 48 and 72 hours after administration of the products.

A single dose, crossover study to assess bioequivalence is considered adequate. According to the SmPC, the tablets are to be swallowed whole with some liquid irrespective of food intake. As such, the fasting condition applied in the study is considered adequate.

Analytical/statistical methods

The analytical method has been adequately validated and is considered acceptable for analysis of the plasma samples. The methods used in this study for the pharmacokinetic calculations and statistical evaluation are considered acceptable.

For baseline correction, for each subject and treatment period, the baseline value was defined as the mean of the -1 hour, -0.5 hour, and pre-dose (0h)) samples obtained before dosing, for that same subject and period. The calculated mean baseline concentration was considered as the pre-dose value. For baseline correction, the baseline value (mean of the three pre-dose samples) was subtracted from each measured concentration, including the pre-dose concentration, meaning that the pre-dose concentration was equal to zero.

Because of the large circulating pool of estrogen as sulfates and glucuronides in humans, unconjugated estradiol, total estrone and unconjugated estrone were quantified in this study and baseline-corrected total estrone was used for bioequivalence assessment.

Results

All 28 subjects completed the study and were included in the analysis.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of baseline corrected total estrone under fasted conditions.

Treatment N=28	AUC_{0-t} (ng.h/ml)	$AUC_{0-\infty}$ (ng.h/ml)	C_{max} (ng/ml)	t_{max} (h)	$t_{1/2}$ (h)
Test	165 ± 58	170 ± 62	18.1 ± 4.0	0.75 (0.5 – 5.0)	13.5 ± 5.2
Reference	168 ± 67	175 ± 75	19.6 ± 4.3	0.75 (0.5 – 4.0)	14.6 ± 4.5
***Ratio (90% CI)**	1.00 (0.95 – 1.05)	--	0.92 (0.85 - 0.99)	--	--
CV (%)	11.1	--	17.5	--	--

$AUC_{0-\infty}$ area under the plasma concentration-time curve from time zero to infinity
AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours
C_{max} maximum plasma concentration
t_{max} time for maximum concentration
$t_{1/2}$ half-life
CV coefficient of variation

**ln-transformed values*

Table 2. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of drospirenone under fasted conditions.

Treatment N=28	AUC_{0-72} (ng.h/ml)	$AUC_{0-\infty}$ (ng.h/ml)	C_{max} (ng/ml)	t_{max} (h)	$t_{1/2}$ (h)
Test	238 ± 39	--	25.5 ± 5.4	1.0 (0.74 – 4.0)	--
Reference	235 ± 55	--	24.3 ± 4.9	1.0 (0.74 – 3.0)	--
***Ratio (90% CI)**	1.02 (0.98 – 1.06)	--	1.04 (0.99 - 1.10)	--	--
CV (%)	8.8	--	12.2	--	--

$AUC_{0-\infty}$ area under the plasma concentration-time curve from time zero to infinity
AUC_{0-72} area under the plasma concentration-time curve from time zero to 72 hours
C_{max} maximum plasma concentration
t_{max} time for maximum concentration
$t_{1/2}$ half-life
CV coefficient of variation

**ln-transformed values*

Conclusion on bioequivalence study

The 90% confidence intervals calculated for AUC_{0-t}/AUC_{0-72} and C_{max} are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the pharmacokinetic parameters of baseline corrected total estrone and drospirenone, Estradiol/Drospirenon Gedeon Richter is considered bioequivalent with Angeliq. Bioequivalence could also be shown for baseline uncorrected total estrone, baseline corrected and uncorrected unconjugated estrone, baseline corrected and uncorrected unconjugated estradiol, supporting the conclusion on bioequivalence.

The MEB has been assured that the bioequivalence study has been conducted in accordance with acceptable standards of Good Clinical Practice (GCP, see Directive 2005/28/EC) and Good Laboratory Practice (GLP, see Directives 2004/9/EC and 2004/10/EC).

IV.3 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/Drospirenon Gedeon Richter.

Table 3. Summary table of safety concerns as approved in RMP

Important identified risks	• Venous and arterial thromboembolic events (including deep vein thrombosis, pulmonary embolism, ischaemic stroke and coronary artery disease) • Oestrogen-dependent cancers such as ovarian or breast cancer • hepatic disorders • gallbladder disorders
Important potential risks	None
Missing information	None

The member states agreed that routine pharmacovigilance activities and routine risk minimisation measures are sufficient for the risks and areas of missing information.

IV.4 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the innovator product Angeliq. No new clinical studies were conducted. The MAH demonstrated through a bioequivalence study that the pharmacokinetic profile of the product is similar to the pharmacokinetic profile of this reference product. Risk management is adequately addressed. This generic medicinal product can be used instead of the reference product.

V. USER CONSULTATION

The MAH submitted a justification for not submitting the results of a readability test. In this justification, the MAH states that the content of the package leaflet (PL) is comparable to the package leaflet of the reference product Angeliq, containing drospirenone and estradiol hemihydrate.
With regard to the design and layout, the MAH submitted a bridging statement explaining that the design and layout of the PL are comparable to the design and layout of the PLs of other products which have successfully been user tested or where bridging regarding design and layout was successfully applied (e.g. in procedure DE/H/3691/001/DC).
The bridging report submitted by the MAH has been found acceptable; bridging is justified for both content and layout of the leaflet.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Estradiol/Drospirenon Gedeon Richter 1 mg/2 mg film-coated tablets has a proven chemical-pharmaceutical quality and is a generic form of Angeliq 1 mg/2 mg film-coated tablets. Angeliq is a well-known medicinal product with an established favourable efficacy and safety profile.

Bioequivalence has been shown to be in compliance with the requirements of European guidance documents.

The Board followed the advice of the assessors.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The member states, on the basis of the data submitted, considered that essential similarity has been demonstrated for Estradiol/Drospirenon Gedeon Richter with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 20 September 2019.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Procedure number	Scope	Product Information affected	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse