CBG MEB

Public Assessment Report

Scientific discussion

Velbienne 2.0 mg/1.0 mg, film-coated tablets

(estradiol valerate/dienogest)

NL/H/3591/001/DC

Date: 19 April 2018

This module reflects the scientific discussion for the approval of Velbienne 2.0 mg/1.0 mg, film-coated tablets. The procedure was finalised on 6 December 2016. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Velbienne 2.0 mg/1.0 mg, film-coated tablets from Exeltis Healthcare S.L.

The product is indicated for hormone replacement therapy (HRT) for estrogen deficiency symptoms in postmenopausal women who are more than one year post menopause.
Experience of 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 Climodien 1/2 mg coated tablets (NL License RVG 24830) which has been registered in by Bayer Pharma B.V, the Netherlands since 13 December 2000.

The concerned member states (CMS) involved in this procedure were Belgium, Spain, France, Luxembourg and Portugal.

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

II. QUALITY ASPECTS

II.1 Introduction

Velbienne is a light pink and rounded tablet. Each film-coated tablet contains: 1.0 mg estradiol valerate (equivalent to 0.764 mg estradiol) and 2.0 mg dienogest

The tablets are packed in PVC/PVDC/aluminium blisters.

The excipients are:
Core - lactose monohydrate, maize starch, pregelatinised maize starch, povidone K30 (E1202) and magnesium stearate (E572).
Coating - polyvinyl alcohol (E1203), titanium dioxide (E171), macrogol/PEG 3350 (E1521), talc (E553b), red iron oxide (E172) and black iron oxide (E172).

II.2 Drug Substances

Dienogest
The active substance dienogest is an established active substance however not described in the European Pharmacopoeia (Ph.Eur.). It is an off-white to slightly yellow powder which is practically insoluble in water and hardly soluble in methanol and acetone. Dienogest shows optical rotation due to the presence of four asymmetric carbons.

The Active Substance Master File (ASMF) procedure is used for dienogest. The main objective of the ASMF procedure, commonly known as the European Drug Master File (EDMF) procedure, is to allow valuable confidential intellectual property or 'know-how' of the manufacturer of the active substance (ASM) to be protected, while at the same time allowing the applicant or marketing authorisation holder (MAH) to take full responsibility for the medicinal product, the quality and quality control of the active substance. Competent Authorities/EMA thus have access to the complete information that is necessary to evaluate the suitability of the use of the active substance in the medicinal product.

Manufacturing process
Dienogest is manufactured in six steps. The overall manufacturing process has been described in sufficient detail for all suppliers. No class 1 solvents or heavy metal catalysts are used in the synthesis from the starting material to dienogest. Dienogest has been adequately characterised, and the used solvents and reagents have acceptable specifications.

Quality control of drug substance
The MAH has adopted the specifications for dienogest as presented in the ASMF of the supplier. In-house methods and specifications are described for the non-compendial tests. The specifications are acceptable in view of the route of synthesis and the various European guidelines. Batch analytical data demonstrating compliance with the drug substance specifications have been provided for three batches.

Stability of drug substance
Stability data for dienogest have been provided for six batches stored at 25°C/60%RH for 60 months and at 40°C/75%RH for 6 months. At long term conditions for at least 60 months and at accelerated conditions for 6 months all parameters comply with the proposed specification and no significant changes have been observed. A re-rest period of 60 months is granted, when stored in the original packaging.

Estradiol valerate
The active substance estradiol valerate is described in the European Pharmacopoeia. It is a white to almost white, crystalline powder which is practically insoluble in water and soluble in ethanol.

The CEP procedure is used for estradiol valerate. 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 European Pharmacopoeia.

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

Quality control of drug substance
The drug substance specification for estradiol valerate is in line with the Ph. Eur. with additional requirements for residual solvents. The specifications as used by the drug product manufacturer are in line with the CEP and the Ph. Eur. and are acceptable. The limits are acceptable.
Batch analytical data demonstrating compliance with the proposed drug substance specification have been provided for three full-scale batches.

Stability of drug substance
The active substance is stable for 5 years when stored under the stated conditions. Assessment thereof was part of granting the CEP and has been granted by the EDQM.

II.3 Medicinal Product

Pharmaceutical development
The pharmaceutical development of the product has been adequately performed; the choice of the active substance and excipients is justified. The test product was compared to the innovator product with respect to active substance, dissolution, and impurity profile. As estradiol valerate is practically insoluble in water, dissolution testing in water did not provide consistent results. Therefore, dissolution studies were done in the presence of a surfactant. Under these conditions similar behaviour was demonstrated for the test and reference product. The batch used in the bioequivalence study has the same quantitative composition and is manufactured according to the proposed manufacturing process. The reference product used in the study is also acceptable. The pharmaceutical development of the product has been adequately described.

Manufacturing process
The dienogest/estradiol valerate tablets are made by a wet granulation and drying process followed by milling, blending, tableting and film-coating. The manufacturing process has been adequately validated according to relevant European guidelines. Validation studies have been performed on three full-scale batches.

Control of excipients
All excipients, including the individual components of the coating system, meet the appropriate regulatory/compendial requirements, and are acceptable.

Quality control of drug product
The product specifications for release and end-of-shelf life for the final products have been provided. The specification includes tests for appearance, identification, average weight, assay for dienogest and estradiol valerate, uniformity of dosage units for dienogest and estradiol valerate, dissolution, related substances, and microbial control. The analytical methods have been adequately described and validated. The specifications are acceptable. Batch analytical results of three pilot-scale batches demonstrating compliance with the specification have been provided.

Stability of drug product
Stability data on the product has been provided for three pilot-scale batches stored at 25°C/60%RH (24 months for two batches and 18 months for one batch) and 40°C/75%RH (6 months). The conditions used in the stability studies are according to the ICH stability guideline. The batches were stored in opaque PVC-PVDC/Aluminium blisters. The data provided shows that no significant changes occur in the parameters tested when the tablets are stored under long term and accelerated conditions. In a photostability study according to ICH Q1B standard, it was shown that the tablets were sensitive to light when unpacked, when packed in their primary packaging the tablets were stable. The proposed shelf-life of 3 years for the drug product is considered acceptable. With the storage condition 'Store in the original package to protect from light'.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
Lactose monohydrate is of animal origin. A TSE/BSE declaration from the supplier has been provided. The lactose comes from milk of healthy animals collected under the same conditions as milk suitable for human consumption.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Velbienne film-coated tablets has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product.
No post-approval commitments were made.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Velbienne 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 Climodien, 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 valerate and Dienogest 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 Velbienne (Exeltis Healthcare S.L., Spain) is compared with the pharmacokinetic profile of the reference product Lafamme tablets (Jenapharm GmbH & Co. KG, Germany).

The choice of the reference product in the bioequivalence study has been justified by comparison of 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 study

Design
A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 32 healthy post-menopausal females (≥ 35 and ≤ 70 years). Each subject received a single dose (1 mg/2 mg) of one of the 2 estradiol valerate/dienogest formulations. There were 2 dosing periods, separated by a washout period of 28 days.

Blood samples were collected at -1 and -0.5 hours prior to dosing, within 5 minutes pre-dose, and at 0.17, 0.25, 0.5, 0.75, 1, 1.25, 1.5, 2, 2.5, 3, 4, 5, 6, 7, 8, 10, 12, 16, 24, 36, 48, and 72 hours after administration of the products.

The design of the study is acceptable. The sampling as well as the frequency of sampling is adequately performed. A study under fasting conditions is appropriate as food does not influence the absorption of the active substances.

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.

Results
Four subjects were withdrawn from the study. One subject was withdrawn prior to study drug administration in Period 2 due to difficulties to install the venous catheter. A second subject was withdrawn due to vomiting within 14 hours after dosing in Period 1. One subject was withdrawn for safety measures due to low hemoglobin level prior to Period 2 study drug administration. Another subject withdrew consent from the study for personal reasons.
One subject was excluded from the analysis because in the second test period blood concentrations of dienogest were below the lower limit of quantification and the concentrations of estrogens were below or equal to the baseline endogenous levels. As a consequence, a total of 27 subjects were included in the analysis.

Table 1. Pharmacokinetic parameters for baseline corrected total estrone, unconjugated estradiol and unconjugated estrone (arrhythmic means ± SD) for each treatment

	Baseline Corrected Total Estrone		**Unconjugated Estradiol**		**unconjugated estrone**	
Treatment	AUC0-t ng•hr/mL	Cmax ng/mL	AUC0-t pg/ml/h	Cmax pg/ml	AUC0-t pg/ml/h	Cmax pg/ml
Test	153 ± 66	15 ± 7	897 ± 375	39.6 ± 73.8	5426 ± 1977	218 ± 70
Reference	139 ± 47	13 ± 5	809.3 ± 301.4	25.3 ± 8.2	5102 ± 1662	213 ± 74
*Ratio (90% CI)	107.% (103- 112%)	114% (104- 124%)	108% (101-115%)	113% (95-134%)	105% (101-- 110%)	103.11% (97- 109)

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

Treatment N=27	**AUC_{0-t}** ng.h/ml	**$AUC_{0-\infty}$** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h	**$t_{1/2}$** h
Test	578.9 ± 153.9	621.9 ± 185.7	55.0 ± 10.5	(0.50 - 4.00)	--
Reference	571.7 ± 134.1	612.9 ± 154.4	52.1 ± 7.3	(0.75 - 3.00)	--
***Ratio (90% CI)**	101% (98-103%)	101% (98-104%)	105 (99-111%)	--	--

$AUC_{0-\infty}$ 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

**ln-transformed values*

Conclusion on bioequivalence study

The choice to determine the baseline corrected estrone levels as primary pharmacokinetic variable is considered acceptable. The 90% confidence intervals of the test/reference ratio for the AUC and C_{max} of dienogest and baseline corrected total estrone were entirely contained within the predefined bioequivalence acceptance limits of 80-125% and therefore bioequivalence can be concluded.

It is noted, however, that the 90% confidence intervals of the test/reference ratio for C_{max} of unconjugated estradiol was 95-134%, and thus outside the bioequivalence acceptance limits of 80-125%. The ANOVA on the ln-transformed data for C_{max} could not detect a statistically significant difference between the treatments which can probably partly be attributed to the high variability of estradiol in combination with the small sample size of the study. The variability for the estradiol C_{max} was high, and the intra subject CV was estimated to be 38.56%. The higher confidence intervals can therefore be accepted.

Overall, based on the submitted bioequivalence study Velbienne is considered bioequivalent with Lafamme tablets.

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 Velbienne.

- Summary table of safety concerns as approved in RMP

Important identified risks	• Breast cancer • Genital bleeding (irregular or unexpected)

	• Venous and arterial thromboembolism • Ovarian cancer
Important potential risks	• Endometrial hyperplasia or cancer • Other sex hormone-related malignancies • Leiomyoma (uterine fibroids) or endometriosis • Benign and malignant liver tumours • Pancreatitis if associated with hypertriglyceridemia • Dementia in women after the age of 65
Missing information	None

The member states agree that routine pharmacovigilance activities are considered sufficient for this product.

IV.4 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the innovator product Climodien. 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 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 test consisted of a pilot test with 4 participants, followed by two rounds with 10 participants each. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability 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

Velbienne 2.0 mg/1.0 mg, film-coated tablets has a proven chemical-pharmaceutical quality and is a generic form of Climodien 1/2 mg coated tablets. Climodien 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 Velbienne with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 6 December 2016.

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
NL/H/3591/1/IA/001	Change in the name and/or address of: a manufacturer (including where relevant quality control testing sites)	-	7-9-2017	Approved	-
NL/H/3591/1/II/002	Updated ASMF version	Y	7-11-2017	Approved	-
NL/H/3591/1/IA/003	European Pharmacopoeial Certificate of Suitability to the relevant Ph. Eur. Monograph.; new certificate from a new manufacturer (replacement or addition)	-	10-1-2018	Approved	-
NL/H/3591/1/IB/004	- Change in the manufacturing process of the finished product, including an intermediate used in the manufacture of the finished product; minor change in the manufacturing process - Change in the batch size (including batch size ranges) of the finished product; up to 10-fold compared to the originally approved batch size	-	12-04-2018	Approved	-
NL/H/3591/001/P/001	Applicants wants to include sections 17 & 18 into the Labelling according to QRD and serialisation rules	Y	24-5-2018	Approved	-