CBG MEB

Public Assessment Report

Scientific discussion

LaFleur 1 mg/2 mg, tablets

(estradiol valerate/dienogest)

NL/H/3130/001/DC

Date: 12 June 2017

This module reflects the scientific discussion for the approval of LaFleur 1 mg/2 mg, tablets. The procedure was finalised on 11 June 2015. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

ASMF	Active Substance Master File
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CMS	Concerned Member State
EDMF	European Drug Master File
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
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 LaFleur 1 mg/2 mg, tablets from Dr. Kade Pharmazeutische Fabrik GmbH.

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 in 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 with reference to the innovator product Climodien 2 mg/2 mg film-coated tablets (NL RVG 24830) which has been registered in the Netherlands by Bayer B.V. since 13 December 2000. Essential similarity is claimed with an innovator product containing 2 mg dienogest and 1 mg estradiol valerate: Lafamme 1 mg/2 mg (NL RVG 32405). This product was first registered in the Netherlands on 2 May 2005 by Bayer B.V. (MRP NL/H/0652/001).

The concerned member state (CMS) involved in this procedure was Germany.

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

II. QUALITY ASPECTS

II.1 Introduction

LaFleur 1 mg/2 mg is a red, uncoated, round tablet and contains as active substances 1.0 mg estradiol valerate (corresponding to 0.76 mg estradiol) and 2.0 mg dienogest.

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

The excipients are: iron oxid red (E172), lactose monohydrate, magnesium stearate, maize starch, povidone K 25 (E1201) and anhydrous colloidal silica.

II.2 Drug Substances

Dienogest
Dienogest is an established active substance, however not described in any Pharmacopoeia. It is an off-white to slightly yellow powder which is practically insoluble in water, hardly soluble in methanol and acetone and soluble in dimethylformamide. Dienogest shows optical rotation due to the presence of four asymmetric carbons. It is manufactured in one crystalline form.

The Active Substance Master File (ASMF) procedure is used for both manufacturers of 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 five steps by both suppliers. The overall manufacturing process has been described in sufficient detail. The manufacturers use acceptable starting material and the process is adequately controlled.

Quality control of drug substance
The MAH has adopted the specifications and methods of both ASMFs with one additional in-house test and a requirement for particle size distribution tested with an in-house method. 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 2 batches for both suppliers.

Stability of drug substance
For one supplier, the proposed re-test of 5 years is acceptable based on available completed 60 months long-term stability studies. No specific temperature restrictions are required as the drug substance is found stable when stored at 25°C/65%RH for this entire period, and for 6 months at 40°C/75%RH.
For the other supplier, a re-test period of 2 years has been accepted, based on available completed 48 months long-term stability studies. No specific temperature restrictions are required as the drug substance is found stable when stored at both 25°C/65%RH and 40°C/75%RH.

Estradiol valerate
Estradiol valerate is an established active substance and described in the European Pharmacopoeia (Ph. Eur.). It is a white to almost white, crystalline powder. The substance is practically insoluble in water and soluble in ethanol. In literature and the Ph. Eur. it is not mentioned that estradiol valerate shows polymorphism.

The CEP procedure is used for both suppliers of the active substance. 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
Two CEPs 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 tests as indicated on the CEPs and an additional specification tested in-house method. Batch analytical data demonstrating compliance with this specification have been provided for two batches for each supplier.

Stability of drug substance
The CEP from supplier one, a re-test period of 5 years was declared for estradiol valerate. No re-test has been indicated on the CEP from supplier two. However, stability testing of two batches demonstrates the stability of the active substance for 12 months stored at 25°C/60%RH and 6 months stored at 40°C/75%RH. Based on the data submitted, a retest period could be granted of 12 months.

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 substances, dissolution, and impurity profile. Dissolution was compared in three pH media. Dienogest dissolved very fast (>85% in 15 minutes) in all media The dissolution results show that estradiol valerate does not dissolve in aqueous media. Therefore, the addition of surfactant to the quality control dissolution medium is acceptable. The results of comparative dissolution are satisfactory.
A thorough discussion on potential degradation impurities for the drug product has been provided. These are adequately controlled.

Manufacturing process
The manufacturing process has been validated according to relevant European/ICH guidelines. The Process manufacturing process has been described in detail with information on mixing equipment and mixing speed and times for each mixing step. The manufacturing process is regarded to be a non-standard process in view of the low dose of the active substances. Validation data on the product have been presented for four full scale batches in accordance with the relevant European guidelines.

Control of excipients
All excipients comply with the Ph. Eur. and are acceptable.

Quality control of drug product
The finished product specifications are adequate to control the relevant parameters for the dosage form. The specification includes tests for appearance, odour, disintegration, identification, assay and uniformity of dosage units for dienogest and estradiol valerate, dissolution, related substances, and microbial control. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product. Satisfactory validation data for the analytical methods have been provided. Batch analytical data of four full scale batches from the proposed production sites have been provided, demonstrating compliance with the specification.

Stability of drug product
The 24-month long-term (25 ± 2°C/60 ± 5% RH) and 6-month accelerated (40°C ± 2°C/75 ± 5%RH) stability results comply and support the shelf-life of 36 months, with no specific storage condition. The studies were performed in accordance with the ICH criteria. Photostability testing results showed that the tablets do not need protection from light.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
Except for lactose monohydrate all excipients are of non-animal origin. Certificates of the manufacturers regarding the TSE-risk of lactose monohydrate have been provided.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that LaFleur 1 mg/2 mg 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 from quality point of view.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since LaFleur 1 mg/2mg 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 Lafamme 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 LaFleur 1 mg/2 mg, tablets (Dr. Kade Pharmazeutische Fabrik GmbH, Germany) is compared with the pharmacokinetic profile of the reference product Lafamme 1 mg/2 mg (Jenapharm GmbH & Co. KG, Germany).
The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

Bioequivalence study

Design
A single-dose, single center, randomized, crossover bioequivalence study was carried out under fasted conditions in 24 healthy postmenopausal female subjects, aged 52-65 years. Each subject received a single dose (1 mg/2 mg) of one of the 2 estradiol valerate/dienogest formulations. Formulations were administered following a controlled fasting of 21 hours. Between periods a wash-out of at least 14 days was maintained.
Blood samples were collected 24 hours and 12 hours before treatment administration (for estradiol only), pre-dose and at 0:20, 0:40, 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 16, 24, 36, 48 and 72 hours post-dose after administration of the products.

The sampling period, wash-out and sampling scheme is adequate with regard to the pharmacokinetic parameters of dienogest and estradiol. 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 method used in this study for the pharmacokinetic calculations and statistical evaluation are considered acceptable.
Results
No subjects withdrew from the study. All 24 participant were included in the analysis.

Table 1. Baseline adjusted pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of estradiol.

Treatment N=24	**AUC_{0-t}** pg/ml/h	**Baseline** pg/ml	**C_{max}** pg/ml	**t_{max}** h	**$t_{1/2}$** h
Test	531 ± 181	1.76 ± 1.92	20.8 ± 5.62	7.0 (4.0-16)	--
Reference	515 ± 174	2.13 ± 1.90	19.6 ± 5.19	1.0 (3.0-16.3)	--
***Ratio (90% CI)**	1.04 (0.96-1.13)	--	1.06 (0.99-1.14)	--	--

$AUC_{0-\infty}$	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*

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

Treatment N=24	**AUC_{0-t}** ng/ml/h	**$AUC_{0-\infty}$** ng/ml/h	**C_{max}** ng/ml	**t_{max}** h	**$t_{1/2}$** h
Test	572 ± 139	--	47.7 ± 7.08	1.0 (0.67-4.0)	--
Reference	570 ± 137	--	49.5 ± 7.37	1.0 (0.67-2.0)	--
***Ratio (90% CI)**	1.00 (0.98-1.03)	--	0.96 (0.90-1.03)	--	--

$AUC_{0-\infty}$	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*

Although the pre-defined acceptance criteria (90% CI within 0.80 – 1.25) for both compounds are met, bioequivalence could not be concluded with these initial results presented by the MAH in the first round of assessment. Bioequivalence should have been established on the estrone metabolites and not estradiol. The estrogen metabolism is complex and it is not possible to distinguish between endogenous estradiol, synthetic estradiol directly absorbed from the tablet and back converted estradiol that originated from the synthetic estradiol.
The MAH agreed to do additional analysis; assessment of baseline-adjusted estrone, estrone sulfate and estrone glucuronide was performed with the plasma samples of the original clinical study.

Table 3. Pharmacokinetic parameters (baseline adjusted, non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of total estrone under fasted conditions.

Treatment N=24	**AUC_{0-t}** nmol/l/h	**$AUC_{0-\infty}$** nmol/l/h	**C_{max}** nmol/l/h	**t_{max}** h	**$t_{1/2}$** h
Test	404 ± 118	411 ± 122	44 ± 14	1.5 (0.67-5.0)	--
Reference	401 ± 111	410 ± 114	45 ± 15	1.0 (0.67-5.0)	--
***Ratio (90% CI)**	1.01 (0.97-1.05)	--	0.98 (0.85-1.12)	--	--

$AUC_{0-\infty}$	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*

<u>Conclusion on bioequivalence study</u>

Long term stability of the analytes in matrix could per definition not be demonstrated, as for this analysis the quality control samples should be stored in the freezer under the same storage conditions

and at least for the same duration as the study samples. It was agreed with the MAH that based on literature data, sample stability is likely to be established for these analytical methods. These sample stability validation tests still had to be performed and data presented at time of registration, hence this was included as a post approval commitment at the end of the DCP procedure: "The long-term frozen sample stability experiment is still under investigation at this moment. Sample storage stability will be performed in July 2015 (8 months), January 2016 (14 months) and June 2016 (19 months) for estrone, estrone sulfate and estrone glucuronide. The experiments should be performed and data should be presented." The commitment has been solved by the applicant in variation procedure NL/H/3130/001/II/006, where the requested long-term frozen sample stability has been shown.

Based on the submitted study LaFleur can be considered bioequivalent with Lafamme. This conclusion is based on equivalent pharmacokinetic profiles for baseline adjusted total estrone of which long term stability is likely to be established. The 90% confidence intervals calculated for AUC_{0-t} and C_{max} for estrone and dienogest are within the bioequivalence acceptance range of 0.80 – 1.25. Furthermore, equivalent pharmacokinetic profiles of the parent estradiol were shown.

Overall, based on the submitted bioequivalence study LaFleur 1 mg/2 mg, tablets 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 LaFleur 1 mg/2 mg, tablets.

- 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 - Leimyoma (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 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 study and experience with the innovator product Lafamme. 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 (PL) 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 PL was German. The study population was selected based on the target population

for LaFleur: female participants, aged 46-64, with varying education levels. The user tested leaflet has been proven clear to the reader. The different sections could be found and understood by the participants.
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

LaFleur 1 mg/2 mg, tablets has a proven chemical-pharmaceutical quality and is a generic form of Lafamme 1/2 mg coated tablets. Lafamme 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 LaFleur 1 mg/2 mg, tablets with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 11 June 2015.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Scope	Procedure number	Type of modification	Date of start of the procedure	Date of end of the procedure	Approval/ non approval	Assessment report attached
Introduction of a summary of pharmacovigilance system, changes in QPPV (including contact details) and/or changes in the Pharmacovigilance System Master File (PSMF) location	NL/H/3130/IA/002	IA	29-12-2015	04-01-2016	Approval	No
Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter such as odour and taste or identification test for a colouring or flavouring material)	NL/H/3130/IA/001/G	IA/G	06-01-2016	05-02-2016	Approval	No
Safety, efficacy and pharmacovigilance changes; to update the SmPC and PIL in accordance with the PRAC signals recommendation	NL/H/3130/1/IA/003	IA	31-03-2016	30-04-2016	Approval	No
Change in the specification parameters and/or limits of the immediate packaging of the finished product; Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter)	NL/H/3130/001/IA/004/G	IA/G	31-03-2016	30-04-2016	Approval	No
Change in batch size (including batch size ranges) of active substance or intermediate used in the manufacturing process of the active substance; Up to 10-fold increase compared to the originally approved batch size Change of specification(s) of a former non EU Pharmacopoeial substance to fully comply with the Ph. Eur. or with a national pharmacopoeia of a Member State; Active substance	NL/H/3130/001/IA/005/G	IA/G	05-08-2016	30-08-2016	Approval	No
Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	NL/H/3130/001/II/006	II	07-11-2016	14-11-2016	Approval	No