LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

# Public Assessment Report
# Scientific discussion

# Dienogest León Farma
# (dienogest)

# SE/H/1789/01/DC
# 2017-1464

**This module reflects the scientific discussion for the approval of Dienogest León Farma. The procedure was finalised on 2018-12-16. For information on changes after this date please refer to the module 'Update'.**

Postadress/Postal address: P.O. Box 26, SE-751 03 Uppsala, SWEDEN
Besöksadress/Visiting address: Dag Hammarskjölds väg 42, Uppsala
Telefon/Phone: +46 (0)18 17 46 00 Fax: +46 (0)18 54 85 66
Internet: www.lakemedelsverket.se E-mail: registrator@lakemedelsverket.se

# I. INTRODUCTION

The application for Dienogest León Farma, 2mg, tablet, is a generic application made according to Article 10(1) of Directive 2001/83/EC. The applicant, Laboratorios León Farma S.A., applies through the Decentralised Procedure with Sweden acting as reference member state (RMS) and AT, CZ, DE, HR, HU, IT, PL and SK as concerned member states (CMS).

The reference medicinal product chosen for the purposes of establishing the expiry of the data protection period is Visanne® 2 mg tabletten, 2 mg, tablet, authorised in NL since 2009, with Bayer B.V. as marketing authorisation holder.

The reference product used in the bioequivalence study is Visanne® tabletta, 2mg, tablet, from HU with Bayer Hungaria Kft as marketing authorisation holder.

For approved indications, see the Summary of Product Characteristics.

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 Discussion on the non-clinical aspects

Since this product has been shown to be essentially similar and refer to a product approved based on a full application with regard to preclinical data, no further such data have been submitted or are considered necessary.

# IV. CLINICAL ASPECTS

## IV.1 Pharmacokinetics

To support the marketing authorisation application the applicant has conducted one bioequivalence study comparing Dienogest, 2 mg, tablet with the reference product Visanne, 2 mg, tablet.

Study 2011-2559

*Methods*

This was a single-dose, two-way crossover study conducted in 28 healthy volunteers, comparing Dienogest, 2 mg, tablet with Visanne, 2 mg, tablet under fasting conditions. Blood samples for concentration analysis were collected pre-dose and up to 60 hours post-dose. Plasma concentrations of dienogest were determined with an LC-MS/MS method. Analysis of variance (ANOVA) was performed on the log-transformed data for $AUC_{0-t}$ and $C_{max}$. The study was conducted between 11th and 27th March 2011.

*Results*

The results from the pharmacokinetic and statistical analysis are presented in

Table **1** below.

**Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, $t_{max}$ median, range) for dienogest, n=27.**

| Treatment | $AUC_{0-t}$ ng*h/ml | $C_{max}$ ng/ml | $t_{max}$ h |
|---|---|---|---|
| **Test** | **571.08 ± 179.83** | **50.72 ± 11.94** | **1.25**<br>**0.50- 3.00** |
| **Reference** | **562.69 ± 154.34** | **55.30 ± 9.65** | **1.00**<br>**0.50- 2.50** |
| ***Ratio (90% CI)** | **100.34**<br>**96.97 - 103.83** | **90.82**<br>**86.59 - 95.26** | **-** |
| **$AUC_{0-t}$** area under the plasma concentration-time curve from time zero to t hours<br>**$C_{max}$** maximum plasma concentration<br>**$t_{max}$** time for maximum plasma concentration | | | |

**calculated based on ln-transformed data*

For $AUC_{0-t}$ and $C_{max}$ the 90% confidence interval for the ratio of the test and reference

products fell within the conventional acceptance range of 80.00-125.00%.

Discussion and overall conclusion
The bioequivalence study and its statistical evaluation were in accordance with accepted standards for bioequivalence testing, as stated in the Guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1/Corr). The bioanalytical methods were adequately validated.

Based on the submitted bioequivalence study, Dienogest, 2 mg, tablet is considered bioequivalent with Visanne, 2 mg, tablet.

## IV.2 Discussion on the clinical aspects

Since this product has been shown to be essentially similar and refer to a product approved based on a full application with regard to clinical efficacy/safety data, no further such data have been submitted or are considered necessary.

## IV.3 Risk Management Plan

The MAH has submitted an updated common risk management plan version 0.2 for Dienogest León Farma, 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 Dienogest León Farma.

***Summary table of safety concerns for Dienogest León Farma:***

| **Table 1: Summary of safety concerns** | |
|---|---|
| Important identified risks | Serious uterine bleeding<br>Bone mineral density loss in adolescents |
| Important potential risks | Depression<br>Reduction of bone mineral density<br>Arterial thromboembolism<br>Venous thromboembolism<br>Ectopic pregnancy<br>Breast cancer<br>Benign and malignant liver tumors<br>Recurrence of cholestatic jaundice<br>Pediatric use |
| Important missing information | Long-term use |

Pharmacovigilance Plan
Routine pharmacovigilance is suggested and no additional pharmacovigilance activities are proposed by the applicant, which is endorsed.

(The MAH provides a specific questionnaire proposed to follow-up on ADRs reporting thromboembolic events.) This is acceptable to the RMS.

Risk minimisation measures
Routine risk minimisation is suggested and no additional risk minimisation activities are proposed by the applicant, which is endorsed.

Summary of the RMP
The RMP version 0.2 for Dienogest León Farma dated 23 July 2018 is acceptable.

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 quality of the generic products, Dienogest León Farma, is found adequate. There are no objections to approval of Dienogest León Farma, from a non-clinical and clinical point of view. Bioequivalence between the test and reference product has been adequately demonstrated. The product information is acceptable.

The application is therefore 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 Dienogest León Farma, 2 mg, tablet was positively finalised on 2018-12-16.

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# Public Assessment Report – Update

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

*Only procedure qualifier, chronological number and grouping qualifier (when applicable)

Postadress/Postal address: P.O. Box 26, SE-751 03 Uppsala, SWEDEN
Besöksadress/Visiting address: Dag Hammarskjölds väg 42, Uppsala
Telefon/Phone: +46 (0)18 17 46 00 Fax: +46 (0)18 54 85 66
Internet: www.lakemedelsverket.se E-mail: registrator@lakemedelsverket.se