COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Dienogest Cyndea Pharma 2 mg tablets

(dienogest)

NL/H/4315/001/DC

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This module reflects the scientific discussion for the approval of Dienogest Cyndea Pharma 2 mg tablets. The procedure was finalised at 26 December 2018. 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 Dienogest Cyndea Pharma 2 mg tablets, from Cyndea Pharma S.L.

The product is indicated for the treatment of endometriosis.

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 Visanne 2 mg, tablets which has been registered in the Netherlands by Bayer B.V. since 21 December 2009.

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

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

II. QUALITY ASPECTS

II.1 Introduction

Dienogest Cyndea Pharma is a white to slightly yellowish, round, tablet with a embossed "D2" on one side. Each tablet contains 2 mg dienogest.

The tablets are packed in PVC/PVDC/Aluminium blister packs.

The excipients are:
Tablet core – lactose monohydrate, povidone K30, pregelatinized maize starch, microcrystalline cellulose, crospovidone, colloidal anhydrous silica, and magnesium stearate.

II.2 Drug Substance

The active substance is dienogest, an established active substance described in the European Pharmacopoeia (Ph.Eur.). It is a white almost white or slightly yellow, crystalline powder and practically insoluble in water. The micronized form of the drug substance is used. Dienogest is a steroid with four stereogenic centres that shows specific optical rotation. Dienogest does not show polymorphism.

The CEP procedure is used for 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 Ph.Eur.

Manufacturing process

A CEP has been submitted; therefore no details on the manufacturing process have been included. Details on the micronization have been included in the dossier by the finished product manufacturer.

Quality control of drug substance

The active substance specification is considered adequate to control the quality and meets the requirements of the monograph in the Ph.Eur with additional requirements for residual solvents and particle size distribution. The specification is acceptable in view of the various European guidelines. Batch analytical data demonstrating compliance with this specification have been provided for three batches.

Stability of drug substance

For the drug substance no retest period and storage conditions have been defined nor supportive stability data have been provided in the dossier. The MAH has declared that the active substance will be tested according to the proposed specification immediately prior to its use in the manufacture of the finished product. This is acceptable.

II.3 Medicinal Product

Pharmaceutical development

The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines. The choice of excipients is justified and their functions explained. The main development studies were the characterisation of the reference product, performance of manufacturing process and formulation optimisation studies and the development of a dissolution method for routine control. Furthermore, comparative dissolution studies were performed in different media within the physiological range between the test and reference batch that were used in the bioequivalence study as well as between the biobatch and several additional drug product batches. The test batch used in the bioequivalence study was manufactured according to the finalised composition and manufacturing process at full production scale and is a representative batch for commercial production. The choices of the packaging and manufacturing process are justified. It has been substantiated that it is not possible to develop a discriminating dissolution test. A very tight dissolution specification has been set. The pharmaceutical development of the product has in general been adequately performed.

Manufacturing process

The manufacturing process has been validated according to relevant European guidelines. The main steps are wet granulation and drying (single-pot), mixing, compression and packaging. Process validation data on the product have been presented for six full scaled batch in accordance with the relevant European guidelines.

Control of excipients

All excipients used in the manufacture of the drug product comply and are controlled in accordance with their respective Ph.Eur. monographs. Adequate requirements have been set for functionality related characteristics, where relevant.

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, identity, assay, dissolution, uniformity of dosage units, loss on drying, related substances and microbiological quality. 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 on six full scaled batches from the proposed production site have been provided, demonstrating compliance with the specification.

Stability of drug product

Stability data on the product have been provided for six full scaled batches stored at 25°C/60% RH (12-24 months), 30°C/75% RH (12-24 months) 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 PVC/PVdC-Al blisters. Photostability studies were performed in accordance with ICH recommendations and showed that the product is not stable when exposed to light. On basis of the stability data, a shelf life could be granted of 24 months. The product should be stored in the outer carton box packaging to protect from light.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies

The drug substance dienogest and all excipients other than lactose monohydrate are from non-animal and non-human origin. The milk used in the production of lactose is sourced from healthy animals in the same conditions as milk collected for human consumption and the lactose is prepared without the use of other ruminant materials than calf rennet.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Dienogest Cyndea Pharma 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 Dienogest Cyndea Pharma 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 Visanne 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

Dienogest is a well-known active substance 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 one bioequivalence study which is discussed below.

IV.2 Pharmacokinetics

The MAH conducted a bioequivalence study in which the pharmacokinetic profile of the test product Dienogest Cyndea Pharma 2 mg tablets (Cyndea Pharma S.L., Spain) is compared with the pharmacokinetic profile of the reference product Visanne 2 mg (Bayer B.V., the Netherlands).

The choice of the reference product in the bioequivalence study has been justified. The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

Bioequivalence study

Design

An open-label, balanced, single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 32 healthy female subjects, aged 22-42 years. Each subject received a single dose (2 mg) of one of the 2 dienogest formulations. The tablet was orally administered with water after a fast of at least 10 hours. There were 2 dosing periods, separated by a washout period of 10 days.

Blood samples were collected pre-dose, and at 0.25, 0.5, 0.75, 1.0, 1.25, 1.5, 1.75, 2, 2.25, 2.5, 3, 3.5, 4, 5, 6, 8, 10, 12, 24, and 36 hours after administration of the products.

The design of the study is acceptable. Dienogest may be taken without reference to food intake. From the literature it is known that food does not interact with the absorption of the active substance. Therefore, a food interaction study is not deemed necessary. The bioequivalence study under fasting conditions is in accordance with CPMP/EWP/QWP/1401/98 Note for Guidance on the investigation of bioavailability and bioequivalence.

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

All 32 subjects completed the study and were eligible for pharmacokinetic analysis.

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

Treatment N=32	**AUC_{0-t} (ng.h/ml)**	**$AUC_{0-\infty}$ (ng.h/ml)**	**C_{max} (ng/ml)**	**t_{max} (h)**	**$t_{½}$ (h)**
Test	1013 ± 217	1244 ± 303	74 ± 15	1.5 (0.75-4.0)	14 ± 3
Reference	962 ± 194	1174 ± 273	70 ± 17	1.5 (0.5-5.0)	14 ± 3
***Ratio (90% CI)**	1.05 (1.02-1.09)	1.06 (1.02-1.10)	1.11 (1.06-1.17)	--	--
CV (%)	7.2	8.6	15.8	--	--

$AUC_{0-\infty}$ 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*

Conclusion on bioequivalence study

The 90% confidence intervals calculated for AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the submitted bioequivalence study Dienogest Cyndea Pharma is considered bioequivalent with Visanne

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 Dienogest Cyndea Pharma.

Table 2. Summary table of safety concerns as approved in RMP

Important identified risks	- Serious uterine bleeding - Reduction of bone mineral density (BMD)
Important potential risks	- Depression - Bone mineral density loss in adolescents - Ectopic pregnancy - Arterial thromboembolism (ATE) - Venous thromboembolism (VTE) - Breast cancer - Benign and malignant liver tumours - Recurrence of cholestatic jaundice
Missing information	- Paediatric use - Long term treatment

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 Visanne. 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 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 PL 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

Dienogest Cyndea Pharma 2 mg tablets has a proven chemical-pharmaceutical quality and is a generic form of Visanne 2 mg, tablets. Visanne 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 Dienogest Cyndea Pharma with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 26 December 2018.

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