COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Dienosis 2 mg tablets

(dienogest)

NL/H/4351/001/DC

Date: 15 August 2019

This module reflects the scientific discussion for the approval of Dienosis 2 mg tablets. The procedure was finalised at 1 May 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

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 Dienosis 2 mg tablets, from Naari BV.

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 states (CMS) involved in this procedure were Germany, Denmark, Sweden 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

Dienosis is a white to off-white, round, flat faced, bevelled edge tablet debossed with “NC” on one side and “22” on the other side. Each tablet contains 2 mg dienogest.

The tablets are packed in blister packs consisting of green PVC/PVDC-film and Aluminium foil film.

The excipients are: lactose monohydrate, microcrystalline cellulose, potato starch, crospovidone (Type A), povidone K25, talc 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. However, a complete dossier is provided about the micronization process, including a detailed description of the process with all operational parameters, the process validation and the test method. Micronization is performed at the same site as the drug substance manufacture.

Quality control of drug substance

The active substance specification is considered adequate to control the quality and is in line with the CEP, 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 full scale batches.

Stability of drug substance

Stability data on the active substance and a conclusion about a proposed re-test period have been provided by the CEP holder (5 years) and the MAH (re-test period of 12 months). Supportive stability data on 11 batches of drug substance have been provided that were stored at 25°C/60% RH (60 months; 3 batches), 30°C/75% RH (6-48 months; 8 batches) and 40°C/75% RH (6 months; 9 batches). Long-term stability data on batches that were analysed according to the Ph.Eur. monograph after its implementation only cover up to 24 months storage. The provided stability data on historical batches as well as batches that were analysed according to and after implementation of the Ph.Eur. monograph, show no trends or changes in any of the tested parameters at all storage conditions. The historical batches were manufactured according to the same process. The overall data provide sufficient confidence that the drug substance will be stable up to the proposed retest period of 5 years. Therefore, no further data are needed and the retest period of 5 years for the CEP holder and 12 months for the finished product manufacturer can be accepted.

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. A compatibility study with dienogest is performed for each excipient alone and for the total mix. Relevant drug substance attributes with a potential impact on the drug product performance are discussed. The acceptance criterion for particle size distribution is not justified by batch analysis results, however as dienogest is

a BCS class I drug, this parameter is not critical and the specification is included only with the aim of uniformity with reference product. Manufacture process development is adequately discussed, with optimisation studies for all relevant process parameters. A standard packaging for this pharmaceutical form has been chosen
Formulation development was aimed at developing a generic product equivalent to the reference product. A dissolution test method has been developed to compare dissolution profiles of reference and test products. The uncomplete dissolution (max 95%) of drug product in the chosen medium is addressed in a degradation study. One bioequivalence study has been performed between the test product Dienosis and the reference product Visanne. Overall, the pharmaceutical development is acceptable.

Manufacturing process
The manufacturing process has been validated according to relevant European guidelines. The main steps are mixing, wet granulation and drying, compression and packaging. Process validation data on the product have been presented for three batches in accordance with the relevant European guidelines.

Control of excipients
The excipients comply with Ph.Eur. requirements. These specifications are acceptable. The need to control functionality related characteristics of the excipients with potential impact on drug product manufacturability, quality and performance is adequately discussed.

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, average mass, resistance to crushing, water determination, dissolution, assay, content uniformity, related substances, microbial enumeration tests. 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 three 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 three full-scale batches stored at 25°C/60% RH (18 months), 30°C/75% RH (12 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 the proposed commercial packaging. Photostability studies were performed in accordance with ICH recommendations and showed that the product is not fully stable when exposed to light. On basis of the stability data, a shelf life could be granted of 18 months. The product should be stored in the original package in order to protect from light.

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

There are no substances of ruminant animal origin present in the product nor have any been used in the manufacturing of this product, so a theoretical risk of transmitting TSE can be excluded.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Dienosis 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 Dienosis 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 Dienosis 2 mg tablets (Naari BV, NL) is compared with the pharmacokinetic profile of the reference product Visanne 2 mg, tablets (Bayer B.V., NL).

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 48 healthy female subjects, aged 46-59 years. Each subject received a single dose (2 mg) of one of the 2 dienogest formulations. The tablet was orally administered with 240 ml 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 0.17, 0.25, 0.5, 0.75, 1, 1.25, 1.5, 1.75, 2, 2.33, 2.67, 3, 3.3, 3.67, 4, 4.5, 5, 6, 8, 12, 16, 24, 36, 48 and 72 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

Four subjects were withdrawn from the study. Three subjects were withdrawn due to adverse events and one subject dropped out. Therefore a total of 44 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=44	AUC_{0-t} (ng.h/ml)	$AUC_{0-\infty}$ (ng.h/ml)	C_{max} (ng/ml)	t_{max} (h)	$t_{½}$ (h)

Test	978.06 ± 229.13	1030.50 ± 247.35	52.86 ± 10.95	2.0 (0.8-6.0)	15.4 ± 2.6
Reference	985.92 ± 234.97	1045.15 ± 259.47	54.59 ± 11.02	1.8 (0.5-6.0)	16.3 ± 3.1
***Ratio (90% CI)**	0.99 (0.97-1.01)	--	0.97 (0.93-1.01)	--	--
CV (%)	5.9	--	11.5	--	--

$AUC_{0-\infty}$ 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*

Conclusion on bioequivalence study

The 90% confidence intervals calculated for AUC_{0-t}, and C_{max} are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the submitted bioequivalence study Dienosis 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 Dienosis.

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

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

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

Dienosis 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 Dienosis with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 1 May 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