COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Dienogest Bailleul 2 mg tablets (dienogest)

NL/H/5647/001/DC

Date: 22 July 2026

This module reflects the scientific discussion for the approval of Dienogest Bailleul 2 mg tablets. The procedure was finalised on 25 October 2023. 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
EMA	European Medicines Agency
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
RMS	Reference Member State
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 Bailleul 2 mg tablets from Laboratoires Bailleul S.A.

The product is indicated for: Treatment of endometriosis.

A comprehensive description of the up-to-date indications and posology is given in the SmPC.

The marketing authorisation has been granted pursuant to Article 10(1) of Directive 2001/83/EC, which concerns a generic application.

In this decentralised procedure, essential similarity is proven between the new product and a European Reference Product (ERP), Visanne 2 mg tablets, which has been registered in the Netherlands via decentralised procedure (NL/H/1569/001/DC) since 21 December 2009.

The concerned member states (CMS) involved in this procedure were France, Germany, Italy and Spain.

II. QUALITY ASPECTS

II.1 Introduction

Dienogest Bailleul is a white to off-white, round, flat faced bevelled edge tablet, debossed with “NC” on one side and “22” on the other side. A tablet contains as active substance 2 mg of dienogest.

The excipients are: lactose monohydrate, microcrystalline cellulose, potato starch, crospovidone (type A), povidone (K-25), talc, and magnesium stearate.

The tablets are packed in blisters of green polyvinyl chloride-polyvinylidene chloride (PVC-PVdC) -film and aluminium foil film.

II.2 Drug Substance

The active substance is dienogest, an established active substance described in the European Pharmacopoeia (Ph.Eur.). The active substance is a crystalline powder and is poorly soluble in water. No polymorphism or stereochemistry issue is relevant for this active substance. A micronised version of the active substance is used in the production of the drug product.

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. The last step of the process, the micronisation, is not covered by the CEP. A complete dossier is provided about the micronisation process, including a detailed description of the process with all operational parameters, the process validation and the test method.

Quality control of drug substance
The active substance specification is in line with the CEP, with additional requirements for particle size distribution and other residual solvents than the ones named in the CEP. The specification is acceptable in view of the route of synthesis and the various European guidelines.
Batch analytical data demonstrating compliance with this specification have been provided for five full scale batches.

Stability of drug substance
The active substance is stable for 12 months 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 product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines.
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.
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.

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.
Manufacture process development is adequately discussed, with optimisation studies for all relevant process parameters. A standard packaging for this pharmaceutical form has been chosen.

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

Control of excipients
The excipients comply with Ph. Eur. requirements and relevant functionality related characteristics are included in the specifications. These specifications 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, identity, average mass, resistance to crushing, water determination, dissolution, assay, content uniformity, related substances and microbial enumeration. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product. An adequate nitrosamines risk evaluation report has been provided. No risk for presence of nitrosamines in the drug product was identified.

Satisfactory validation data for the analytical methods have been provided.

Batch analytical data from nine exhibit scale batches and three commercial scale 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 nine batches stored at 25°C/ 60% RH (24 months), 30°C/65% RH (12 months) and 40°C/75% RH (6 months). The stability was tested in accordance with applicable European guidelines. Photostability studies were performed in accordance with ICH requirements and showed that the product is not fully stable when exposed to light. On basis of the data submitted, a shelf life was granted of 2 years. On 28 April 2025, a variation procedure (NL/H/5647/001/IB/001) was approved, granting a new shelf life of 3 years (see "'steps taken after finalisation' at the end of this PAR). The labelled storage conditions are to "Store in the original packaging 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 Dienogest Bailleul 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 Bailleul is intended for generic substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment was 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 was made to the preclinical data obtained with the innovator product. A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which was 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 member states agreed that no further clinical studies are required, besides 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 2 mg tablets (Laboratoires Bailleul S.A, Luxembourg) was compared with the pharmacokinetic profile of the reference product Visanne 2 mg tablets (Bayer B.V., the Netherlands).

The choice of the reference product in the bioequivalence study has been justified by comparison of dissolution study results and composition. The formula and preparation of the bioequivalence batch was identical to the formula proposed for marketing.

Bioequivalence study BE/17/484

Design

A single-dose, open-label, balanced, randomised, two-period, two-treatment, two-sequence, two-way 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 two dienogest formulations. The tablet was orally administered with 240 ml water after a

fasting period of at least 10 hours. There were two 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, 3.33, 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 dienogest. 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
Three subjects were withdrawn from the study due to adverse events (high blood pressure), one subject did not report for period II. The remaining 44 subjects were eligible for pharmacokinetic analysis.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of dienogest, 2 mg 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)
Test	978 ± 229	1031 ± 247	53 ± 11	2.00 (0.80-6.00)
Reference	986 ± 235	1045 ± 260	55 ± 11	1.80 (0.50-6.00)
***Ratio (90% CI)**	0.99 (0.97 – 1.01)	-	0.97 (0.93 – 1.01)	-

$AUC_{0-\infty}$	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 = 72 hours
C_{max}	Maximum plasma concentration
t_{max}	Time after administration when maximum plasma concentration occurs
CI	Confidence interval

**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 Bailleul 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 Bailleul. At the time of approval, the most recent version of the RMP was version 0.2 dated 10 March 2023.

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

Important identified risks	None
Important potential risks	None
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 studies and experience with the innovator product Visanne. 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 English.

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 Bailleul 2 mg tablets has a proven chemical-pharmaceutical quality and are 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 Bailleul with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 25 October 2023.

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/5647/001 /IB/001	Change in the shelf-life or storage conditions of the finished product - Extension of the shelf life of the finished product - As packaged for sale (supported by real time data)	Yes	28-4-2025	Approved	N/A
NL/H/5647/001 /IA/002	Submission of a new or updated Ph. Eur. certificate of suitability or deletion of Ph. Eur. certificate of suitability: For an active substance, For a starting material/reagent/ intermediate used in the manufacturing process of the active substance, For an excipient - European Pharmacopoeial Certificate of Suitability to the relevant Ph. Eur. Monograph - Updated certificate from an already approved manufacturer	No	21-5-2025	Approved	N/A
NL/H/5647/001 /IA/003	Introduction of, or changes to, a summary of pharmacovigilance system for medicinal products for human use - Introduction of a summary of pharmacovigilance	No	1-7-2025	Approved	N/A

	system, changes in QPPV (including contact details) and/or changes in the Pharmacovigilance System Master File (PSMF) location				
NL/H/5647/001 /IB/004	Change in the (invented) name of the medicinal product - for Nationally Authorised products	Yes	28-8-2025	Approved	N/A
NL/H/5647/001 /IA/005	Replacement or addition of a manufacturing site for part or all of the manufacturing process of the finished product - Secondary packaging site	No	24-9-2025	Approved	N/A
NL/H/5647/001 /IB/006	Change in the (invented) name of the medicinal product - for Nationally Authorised products	Yes	8-1-2026	Approved	N/A