COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Lumivela 0.150 mg/0.02 mg and 0.150 mg/0.03 mg film-coated tablets

(desogestrel/ethinylestradiol)

NL/H/4041/001-002/DC

Date: 17 October 2018

This module reflects the scientific discussion for the approval of Lumivela 0.150 mg/0.02 mg and 0.150 mg/0.03 mg film-coated tablets. The procedure was finalised at 13 June 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 Lumivela 0.150 mg/0.02 mg and 0.150 mg/0.03 mg film-coated tablets, from Exeltis Healthcare S.L.

The product is indicated for oral contraception.
A comprehensive description of the indications and posology is given in the SmPC.

For the lowest strength the MAH claimed essential similarity with Mercilon 0.15/0.02 mg, tablets (NL License RVG 11508) which has been registered in the Netherlands by N.V. Organon since 19 November 1987.
For the highest strength, essential similarity is claimed with the innovator product Marvelon 0.15/0.03 mg tablets (NL License RVG 08859) which has been registered in the Netherlands by N.V. Organon since 29 May 1981.

The concerned member states (CMS) involved in this procedure were Belgium, Finland and Luxembourg.

The marketing authorisation has been granted pursuant to Article 10(3) of Directive 2001/83/EC, a hybrid application. The presence of the seven placebo tablets in the applied product, which are not registered for the reference product, justifies the legal basis of Article 10(3) hybrid application.

II. QUALITY ASPECTS

II.1 Introduction

Lumivela consists of active and placebo tablets. The active tablets are white, round, film-coated tablets coded with on one side “C” and on the reverse side “5” (0.15 mg/0.02 mg strength) or “7” (0.15 mg/0.03 mg strength). The placebo tablets are green, round, film-coated tablets.

The active tablets contain 150 micrograms of desogestrel and 20 or 30 micrograms of ethinylestradiol.

The film-coated tablets are packed in blisters of aluminium push-through foil and clear to slight opaque PVC/PVDC film.

The excipients in the active tablets are:

Tablet core - Lactose monohydrate, maize starch, povidone K-30 (E1201), RRR-Alpha-tocopherol (E307), soybean oil, silica colloidal hydrated (E551), silica colloidal anhydrous (E551) and stearic acid (E570)
Tablet coating – Hypromellose 2910 (E464), macrogol 400 and titanium dioxide (E171)

The excipients in the placebo tablets are:
Tablet core - Lactose monohydrate, maize starch, povidone K-30 (E1201), silica colloidal anhydrous (E551) and magnesium stearate (E572). Tablet coating - Hypromellose 2910 (E464), triacetin (E151
8), polysorbate 80, titanium dioxide (E171), FD & C Blue 2 Aluminium lake (E132) and yellow iron oxide (E172)

II.2 Drug Substances

The active substances are desogestrel and ethinylestradiol, established active substances, described in the European British Pharmacopoeia (Ph.Eur.).

The CEP procedure is used for both active substances. 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.

Desogestrel
The active substance desogestrel is a white or almost white crystalline powder. It is practically insoluble in water and has six chiral centres but does not exhibit polymorphism.

Manufacturing process
A CEP has been submitted; therefore no details on the manufacturing process have been included.

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 tests on residual solvents and particle size. Batch analytical data demonstrating compliance with this specification have been provided for three batches.

Stability of drug substance
The active substance is stable for three years when stored under the stated conditions. Assessment thereof was part of granting the CEP and has been granted by the EDQM.

Ethinylestradiol

The active substance ethinylestradiol is a white or slightly yellowish-white, crystalline powder. It is practically insoluble in water, freely soluble in ethanol and dissolves in dilute alkaline solutions.

Manufacturing process

CEPs have been submitted; therefore no details on the manufacturing process have been included.

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 tests on residual solvents and particle size. Batch analytical data demonstrating compliance with this specification have been provided for three batches per manufacturer.

Stability of drug substance

The active substance is stable for 5 years or 4 years (depending on manufacturer) when stored under the stated conditions. Assessment thereof was part of granting the CEPs 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. The choice of excipients is justified and their functions are explained. RRR-α-tocopherol was selected as antioxidant to avoid degradation of desogestrel. This choice and concentration was made based on the qualitative composition of the reference products.

Bioequivalence was shown *in vivo* for both strengths The concomitant comparative *in vitro* dissolution data do not support bioequivalence. Dissolution of ethinylestradiol was not similar at pH 1.2 for both strengths and at pH 6.8 for the 0.15 mg/0.03 mg strength and dissolution of desogestrel could not be determined at the three pH due to technical constraints. However, bioequivalence *in vivo* prevails over these data.

Manufacturing process

The manufacturing process is a direct compression process and has been validated according to relevant European guidelines. It consists of pre-blending, mixing, tabletting, coating and packaging. The product is manufactured using conventional manufacturing techniques, but given the low concentration of active substance in the drug product, the manufacturing process can be considered as non-standard. Process validation data on the product have been presented for two batches for the 0.15 mg/0.02 mg strength and one batch for the 0.15 mg/0.03 mg strength batches in accordance with the relevant European guidelines.

Control of excipients

Where possible, excipients are tested in accordance with their respective Ph.Eur. monograph. In-house specifications are provided for the coating mixtures.

RRR-α-tocopherol consists of a mixture of RRR-α-tocopherol with soy bean oil. A specification has been set for this mixture in line with the USP monograph for vitamin E preparations and additional requirements as stated in the Food Chemical Codex (USA). RRR-α-tocopherol is absorbed to silica. The specification for silica has been set as per Ph.Eur. monograph. No separate specifications have been included for the individual components of the RRR-α-tocopherol mixture. Overall, the 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, identification, assay, dissolution, uniformity of dosage units, 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 three pilot scale and three full scale batches of the 0.15 mg/0.02 mg 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 pilot scale and three full scale batches of the 0.15 mg/0.02 mg strength stored at 25°C/60% RH (pilot scale batches for 36 months, full scale batches for 24 months), 30°C/ 65% RH (12 months) and 40°C/75%RH (6 months) and six full scale batches of the 0.15 mg/0.03 mg strength stored at 25°C/60% RH (36 and 12 months), 30°C/ 65% RH (12 months) and 40°C/75%RH (6 months). The conditions used in the stability studies are according to the ICH stability guideline. Significant changes in desogestrel and/or ethinylestradiol assay without concomitant increases in impurity levels were observed at all storage conditions of the 0.15 mg/0.02 mg strength and at accelerated conditions for the 0.15 mg/0.03 mg strength. A suitable explanation has been provided for these findings. Photo stability studies are carried out under ICH conditions. Overall, the tested parameters are considered to be stability indicating. Based on the provided stability data, a shelf life of 24 months and storage conditions “Do not store above 30°C. Store in the original package in order to protect from light.” are justified.

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

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies: A TSE declaration has been provided by the MAH for lactose monohydrate as it is of animal origin. Stearic acid is of vegetable origin.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Lumivela has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Lumivela is intended for hybrid 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 hybrid formulation of Mercilon and Marvelon which are 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

Ethinylestradiol and desogestrel are 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 two bioequivalence studies, which are discussed below.

IV.2 Pharmacokinetics

The MAH conducted two bioequivalence studies in which the pharmacokinetic profile of the test product Lumivela 0.150 mg/0.02 mg film-coated tablets (Exeltis Healthcare S.L, Spain) is compared with the pharmacokinetic profile of the reference product Mercilon 0.15/0.02 mg, tablets (Organon, the Netherlands) and Lumivela 0.150 mg/0.03 mg film-coated tablets

(Exeltis Healthcare S.L, Spain) with Marvelon 0.15/0.03 mg tablets (Organon, 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.

The design of the studies are acceptable. The sampling period and sampling scheme are adequate to properly estimate pharmacokinetic parameters. The measurement of the metabolite 3-keto-desogestrel is justified by the achievement of non measurable plasma concentrations of the parent compound desogestrel in this study. A declaration on GCP compliance is present

For the desogestrel component, bioequivalence will be based on the active metabolite 3-keto-desogestrel (etonogestrel), as it can reasonably be assumed that no measurable plasma concentrations of the parent compound desogestrel will be achieved in this study. Measurement of 3-keto-desogestrel will be truncated at 72 hours as a result of its long half life.

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.

Bioequivalence studies
Bioequivalence study I - 0.150 mg/0.02 mg under fasting conditions
Design
A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 60 healthy female subjects of child bearing potential or pre-menopausal females with tubal ligation, aged 21-45 years. Each subject received a single dose (0.150 mg/0.02 mg) of one of the 2 ethinylestradiol and desogestrel formulations. The tablet was orally administered with 240 ml water after an overnight fast. There were 2 dosing periods, separated by a washout period of 28 days.

Blood samples were collected at pre-dose and at 0.3, 0.7, 1, 1.25, 1.5, 1.75, 2, 2.25, 2.5, 3, 4, 6, 8, 12, 16, 24, 36, 48 and 72 hours after administration of the products.

Results
Two subjects were withdrawn from the study due to vomiting and personal reasons. A total of 58 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 ethinylestradiol under fasted conditions.

Treatment N=58	AUC_{0-t} (pg.h/ml)	$AUC_{0-\infty}$ (pg.h/ml)	C_{max} (pg/ml)	t_{max} (h)
Test	710 ± 249	772 ± 356	69 ± 21	1.5 (1.0-2.5)
Reference	711 ± 215	754 ± 220	74 ± 22	1.5 (1.0-2.25)
***Ratio (90% CI)**	0.99 (0.95-1.03)	1.00 (0.95-1.05)	0.93 (0.89-0.96)	--

$AUC_{0-\infty}$ 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

**ln-transformed values*

Table 2. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of 3-keto-desogestrel under fasted conditions.

Treatment N=58	AUC_{0-t} (pg.h/ml)	$AUC_{0-\infty}$ (pg.h/ml)	C_{max} (pg/ml)	t_{max} (h)
Test	9764 ± 3848	--	1340 ± 391	1.25 (0.7-3.0)
Reference	10229 ± 4526	--	1409 ± 490	1.5 (1.0-4.0)
***Ratio (90% CI)**	0.97 (0.94-0.99)	--	0.99 (0.91-1.04)	--

$AUC_{0-\infty}$ 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

**ln-transformed values*

Bioequivalence study II - 0.150 mg/0.03 mg under fasting conditions

Design

A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 60 healthy female subjects of child bearing potential or pre-menopausal females with tubal ligation, aged 20-45 years. Each subject received a single dose (0.150 mg/0.03 mg) of one of the 2 ethinylestradiol and desogestrel formulations. The tablet was orally administered with 240 ml water after an overnight fast. There were 2 dosing periods, separated by a washout period of 28 days.

Blood samples were collected at pre-dose and at 0.3, 0.7, 1, 1.25, 1.5, 1.75, 2, 2.25, 2.5, 3, 4, 6, 8, 12, 16, 24, 36, 48 and 72 hours after administration of the products.

Results

One subject withdrew consent and two subjects were withdrawn due to impossibility to obtain blood samples and receiving concomitant medication that could have impact on the

pharmacokinetic profile of desogestrel. One subject was excluded from the analysis due to pre-dose levels of more than 5% of the maximum plasma concentration. A total of 56 subjects completed the study and were eligible for pharmacokinetic analysis.

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

Treatment N=56	AUC_{0-t} (pg.h/ml)	$AUC_{0-\infty}$ (pg.h/ml)	C_{max} (pg/ml)	t_{max} (h)
Test	463 ± 150	503 ± 166	45 ± 13	1.5 (1.0-2.5)
Reference	475 ± 164	514 ± 175	48 ± 16	1.5 (1.0-3.0)
***Ratio (90% CI)**	0.98 (0.95-1.01)	0.98 (0.95-1.02)	0.93 (0.90-0.96)	--

$AUC_{0-\infty}$ 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

**ln-transformed values*

Table 4. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of 3-keto-desogestrel under fasted conditions.

Treatment N=56	AUC_{0-t} (pg.h/ml)	$AUC_{0-\infty}$ (pg.h/ml)	C_{max} (pg/ml)	t_{max} (h)
Test	9908 ± 3385	--	1421 ± 442	1.25 (1.0-4.0)
Reference	10471 ± 3499	--	1525 ± 433	1.5 (1.0-4.0)
***Ratio (90% CI)**	0.93 (0.91-0.97)	--	0.92 (0.87-0.97)	--

$AUC_{0-\infty}$ 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

**ln-transformed values*

Conclusion on bioequivalence studies

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 studies Lumivela is considered bioequivalent with Mercilon and Marvelon.

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 Lumivela.

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

Important identified risks	- Venous thromboembolism - Arterial thromboembolism - Benign and malign liver tumours - Breast cancer, Cervical cancer - Effect on hereditary angioedema - Disturbance of liver function - Pancreatitis - Increased blood pressure
Important potential risks	- Worsening of endogenous depression/depressed mood - Crohn's disease and ulcerative colitis
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 Mercilon and Marvelon. 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 hybrid medicinal product can be used instead of the reference product.

V. USER CONSULTATION

A user consultation with target patient groups on the package leaflet (PL) has been performed on the basis of a bridging report making reference to Bellvalyn 150/20 and 150/30 micrograms, film-coated tablets (NL/H/2754/001-002/DC). The bridging report submitted by the MAH has been found acceptable; bridging is justified for both content and layout of the leaflet.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Lumivela 0.150 mg/0.02 mg and 0.150 mg/0.03 mg film-coated tablets have a proven chemical-pharmaceutical quality and are hybrid forms of Mercilon 0.15/0.02 mg, tablets and Marvelon 0.15/0.03 mg tablets. Mercilon and Marvelon are a well-known medicinal products 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 Lumivela with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 13 June 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