COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Liberelle 0.25 mg/0.035 mg tablets

(norgestimate/ethinylestradiol)

NL/H/4134/001/DC

Date: 4 April 2019

This module reflects the scientific discussion for the approval of Liberelle 0.25 mg/0.035 mg tablets. The procedure was finalised at 20 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
VTE	Venous Thromboembolism

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Liberelle 0.25 mg/0.035 mg tablets, from Exeltis Healthcare S.L.

The product is indicated for oral contraception.

The decision to prescribe this product should take into consideration the individual woman's current risk factors, particularly those for venous thromboembolism (VTE), and how the risk of VTE with Liberelle compares with other combined hormonal contraceptives.

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 Cilest film-coated tablets norgestimaat/ethinylestradiol 0.250mg/0.035mg (NL License RVG 12846) which has been registered in The Netherlands by Janssen-Cilag B.V. since 21 May 1990.

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

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

II. QUALITY ASPECTS

II.1 Introduction

Liberelle is a blue cylindrical biconvex tablet. Each tablet contains 250 micrograms of norgestimate and 35 micrograms of ethinylestradiol.

The tablets are packed in PVC/PVDC/Al blister strips.

The excipients are: maize starch, lactose monohydrate, magnesium stearate and indigo carmine (E132).

II.2 Drug Substances

Ethinylestradiol
The active substance is ethinylestradiol, an established active substance described in the European Pharmacopoeia (Ph.Eur.). It is a white to slightly yellowish-white crystalline

powder. The active substace is practically insoluble in water, freely soluble in ethanol (96%) and dissolves in dilute alkaline solutions. Ethinylestradiol exhibits polymorphism, two polymorphic forms of ethinylestradiol are known. Form I is consistently used.

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.

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 in-house methods for 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 5 years when stored under the stated conditions. Assessment thereof was part of granting the CEP and has been granted by the EDQM.

Norgestimate

The active substance is norgestimate, an established active substance described in the European Pharmacopoeia (Ph.Eur.). It is a white to off-white or yellowish crystalline powder. Norgestimate is practically insoluble in water, freely soluble in methylene chloride and soluble in acetone. The active substance does not show polymorphism, however does shows isomerism.

The Active Substance Master File (ASMF) procedure is used for the active substance. The main objective of the ASMF procedure, commonly known as the European Drug Master File (EDMF) procedure, is to allow valuable confidential intellectual property or 'know-how' of the manufacturer of the active substance (ASM) to be protected, while at the same time allowing the applicant or marketing authorisation holder (MAH) to take full responsibility for the medicinal product, the quality and quality control of the active substance. Competent Authorities/EMA thus have access to the complete information that is necessary to evaluate the suitability of the use of the active substance in the medicinal product.

Manufacturing process
At least four full chemical steps follow after introduction of this starting material. The starting materials, intermediates and reagents are adequately characterised and are acceptable.

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. Batch analytical data demonstrating compliance with this specification have been provided for three micronized and three non-micronized batches.

Stability of drug substance
Stability data on the active substance have been provided for three micronized batches stored at 30°C/75% RH (9 months) and 40°C/75% RH (6 months). In view of the particle size of norgestimate in the test bio-batch it is concluded that only the micronized quality is relevant for the drug substance at issue as used for the drug product. For all test parameters the specifications were met. In view of this, the proposed re-test period of 1 year for micronized norgestimate is considered acceptable. The drug substance does not require specific storage conditions.

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. It is strongly based on the composition and dissolution behaviour of the originator product Cilest. A bioequivalence study has been performed. The test and reference bio-batches have been compared in dissolution studies in pH 1.2, pH 4.5, pH 6.8 and the QC test medium (see above), all with 75 rpm paddle speed. All dissolution profiles between test and reference product are very similar: either similarity factor f2 are >50, or dissolution results were >85% in 15 min. Overall, the pharmaceutical development has been adequately described.

Manufacturing process
The manufacturing process consists of wet-granulation, tabletting and packaging and has been validated according to relevant European guidelines. Process validation data on the product have been presented for two batches at minimum size and one batch at maximum size in accordance with the relevant European guidelines.

Control of excipients
All excipients except the colourant meet the requirements of the concerning Ph. Eur. monograph. The colourant Indigo carmine meets the requirements as listed in Commission Regulation (EU) No. 231/201. 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, average weight, uniformity of weight, resistance to crushing, friability, disintegration, dissolution, assay, uniformity of dosage, related substances, colouring identification, loss on drying and microbial control. 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 from six 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 validation batches stored at 25°C/60% RH (24 months) and 30°C/65% RH (12 months) and 40°C/75% RH (6 months). The batches were stored in accordance with applicable European guidelines and the proposed packaging. Photo stability study results showed that the product is sensitive to light.
On basis of the data submitted, a shelf life was granted of 2 years. The labelled storage conditions are: 'Store below 30°C. Store in original package to protect from light'.

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

For the two lactose monohydrate qualities adequate BSE/TSE statements have been provided. For magnesium stearate it has been stated that stearic acid used for this excipient is from vegetable origin.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Liberelle 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 Liberelle 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 Cilest 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

Ethinylestradiol and norgestimate 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 a bioequivalence study, which is discussed below.

IV.2 Pharmacokinetics

The MAH conducted a bioequivalence study in which the pharmacokinetic profile of the test product Liberelle 0.25 mg/0.035 mg tablets (Exeltis Healthcare S.L, Spain) is compared with the pharmacokinetic profile of the reference product Cilest film-coated tablets norgestimaat/ethinylestradiol 0.250mg/0.035mg (Janssen-Cilag B.V., The Netherlands).

The choice of the reference product in the bioequivalence study has been justified by comparison of dissolution results and compositions of reference products (if applicable) in different member states. The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

Bioequivalence study

Design

A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 24 healthy female subjects, aged 26-45 years. Each subject received a single dose (0.25 mg/0.035 mg) of one of the 2 ethinylestradiol/norgestimate formulations. The tablet was orally administered with 240 ml water after an overnight fast of at least 10 hours. There were 2 dosing periods, separated by a washout period of 28 days.

Blood samples were collected at pre-dose and at 0.333, 0.667, 1.00, 1.25, 1.50, 1.75, 2.00, 3.00, 4.00, 6.00, 8.00, 12.0, 16.0, 24.0, 36.0, 48.0 and 72.0 hours after administration of the products.

The design of the study is acceptable. 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.
Study samples were analysed for levels of both 17-desacetylnorgestimate and ethinylestradiol. The MAH provided references to demonstrate that the parent compound norgestimate cannot be reliably determined in plasma, since plasma concentrations were below the lower limit of quantification (0.1 ng/mL). There are however examples in recent literature where the parent compound norgestimate could be determined in plasma. Therefore, demonstrating bioequivalence using norelgestromin (17-deacetyl Norgestimate), the active and first metabolite, is considered acceptable.

Results
One subject withdrew consent. Therefore, 23 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=23	**AUC_{0-t}** (pg.h/ml)	**$AUC_{0-\infty}$** (pg.h/ml)	**C_{max}** (pg/ml)	**t_{max}** (h)
Test	731.9 ± 191.3	771.7 ± 197.5	73.8 ± 18.9	1.5 (0.7 – 3.0)
Reference	794.9 ± 215.3	842.4 ± 226.25	77.5 ± 19.0	1.5 (1.0 – 2.0)
***Ratio (90% CI)**	0.92 (0.88 – 0.97)	--	0.95 (0.89 – 1.01)	--
CV (%)	9.55	--	12.96	--

$AUC_{0-\infty}$ 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
CV coefficient of variation

**ln-transformed values*

Table 2. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of 17-deacetylnorgestimate under fasted conditions.

Treatment N=23	AUC_{0-t} (pg.h/ml)	$AUC_{0-\infty}$ (pg.h/ml)	C_{max} (pg/ml)	t_{max} (h)
Test	14704.9 ± 4784.7	17477.2 ± 5206.3	1612.8 ± 445.6	1.5 (1.0 – 3.1)
Reference	16.589.5 ± 4654.7	19446.3 ± 6041.1	1725.1 ± 16.1	1.3 (1.0 – 3.0)
***Ratio (90% CI)**	0.87 (0.83 – 0.92)	--	0.91 (0.84 – 0.99)	--
CV (%)	10.15	--	17.12	--

$AUC_{0-\infty}$ 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
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 Liberelle is considered bioequivalent with Cilest.

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 Liberelle.

Table 3. Summary table of safety concerns as approved in RMP

Important identified risks	- Venous thromboembolic events - Arterial thromboembolic events
Important potential risks	- Depression - Increased blood pressure - Breast cancer - Pancreatitis - Benign and malignant liver tumours - Worsening of Crohn's disease and Ulcerative colitis - Cervical cancer - Angioedema - Insulin resistance/decreased glucose tolerance

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 Cilest. 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 2 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

Liberelle 0.25 mg/0.035 mg tablets has a proven chemical-pharmaceutical quality and is a generic form of Cilest film-coated tablets norgestimaat/ethinylestradiol 0.250mg/0.035mg. Cilest 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 Liberelle with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 20 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