CBG MEB

Public Assessment Report

Scientific discussion

Etonogestrel/Ethinylestradiol Leon Pharma 0.120 mg/0.015 mg per 24 hours, vaginal delivery system

(etonogestrel/ethinylestradiol)

NL/H/3722/001/DC

Date: 10 October 2017

This module reflects the scientific discussion for the approval of Etonogestrel/Ethinylestradiol Leon Pharma 0.120 mg/0.015 mg per 24 hours, vaginal delivery system. The procedure was finalised on 18 May 2017. 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
ATE	Arterial thromboembolic events
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHC	Combined Hormonal Contraceptives
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 thromboembolic events

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Etonogestrel/Ethinylestradiol Leon Pharma 0.120 mg/0.015 mg per 24 hours, vaginal delivery system from Laboratorios León Farma S.A.

The product is indicated for contraception. Etonogestrel/Ethinylestradiol Leon Pharma is intended for women of fertile age. The safety and efficacy have been established in women aged 18 to 40 years.

The decision to prescribe Etonogestrel/Ethinylestradiol Leon Pharma should take into consideration the individual woman's current risk factors, particularly those for venous thromboembolism (VTE), and how the risk of VTE with Etonogestrel/Ethinylestradiol Leon Pharma compares with other combined hormonal contraceptives (CHCs) (see SmPC sections 4.3 and 4.4).

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 NuvaRing 0.120 mg/0.015 mg per 24 hour vaginal delivery system which has been registered by N.V. Organon (NL Licence RVG 25073) in the Netherlands through procedure NL/H/0265/001 since 14 February 2001.

The concerned member states (CMS) involved in this procedure were Austria, Belgium, Germany, Spain, France, Italy, Luxembourg, Norway, Poland and Portugal.

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

II. QUALITY ASPECTS

II.1 Introduction

Etonogestrel/Ethinylestradiol Leon Pharma is a flexible, transparent, and colourless to almost colourless ring.

The vaginal delivery system contains 11.0 mg etonogestrel and 3.474 mg ethinylestradiol. The ring releases etonogestrel and ethinylestradiol at an average amount of 0.120 mg and 0.015 mg, respectively per 24 hours, over a period of three weeks.

Etonogestrel/Ethinylestradiol Leon Pharma is packed in a sachet, which is made of PET/Aluminium/LDPE.

The excipients are ethylene vinylacetate copolymer, 28% vinylacetate and polyurethane.

II.2 Drug Substance

Ethinylestradiol
The active substance is ethinylestradiol, an established active substance described in the European Pharmacopoeia (Ph.Eur.). Ethinylestradiol is a white or slightly yellowish-white, crystalline powder. The hemihydrate form is adequately limited.

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. Batch analytical data demonstrating compliance with this specification have been provided for three batches.

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

Etonogestrel
The active substance is etonogestrel, an established active substance that is not described in the European Pharmacopoeia (Ph.Eur.). Etonogestrel is a white to almost white crystalline powder. It has six chiral centres. Polymorphic forms have not been observed.

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
Etonogestrel is manufactured through seven full chemical steps and two purification steps. The starting material is obtained after five preceding steps including two fermentation steps. Sufficient information is provided about the manufacturing process. The impurities in the starting material are fully explained, and possible carry-over has been discussed. The specifications for the starting material are adequate.

Quality control of drug substance
The active substance specification is considered adequate to control the quality. Batch analytical data demonstrating compliance with this specification have been provided for three batches.

Stability of drug substance
Stability data on the active substance have been provided for three micronized and three non-micronized batches. The micronized batches have been stored up to 36 months at 25°C/60% RH and six months at 40°C/75% RH. The non-micronized batches have been stored for 60 months at 25°C/60% RH and six months at 40°C/75% RH. Based on the data submitted, a retest period could be granted of two years when stored in the original package to protect from light. The product does not require special temperature 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. Most essential for drug release rate of both active substances is a membrane-controlled release. A linear correlation between daily release and the thickness of the skin is shown. Additional data on the robustness of the formulation have been provided, the variation range is acceptable. Critical parameters of the membrane have been adequately discussed. The manufacturing process development based on the co-extrusion process is also accepted.

The amounts of the active substances are slightly different between the generic and innovator product. Hence Etonogestrel/Ethinylestradiol Leon Pharma contains 11.0 mg etonogestrel and 3.474 mg ethinylestradiol, while NuvaRing contains 11.7 mg etonogestrel and 2.7 mg ethinylestradiol. However both products release the active substances at an average rate of 0.120 mg and 0.015 mg per 24 hours, over a period of three weeks.

An adequate development report on the *in vitro* elution method has been provided, including an accurate description. Its discriminative ability and its predictive bio-relevant value are satisfactory resolved. The established in vitro in vivo correlation (IVIVC) model was not fully validated. However, the model is considered supportive for the setting of the *in vitro* elution specification limits for both active substances.

One bioequivalence study has been carried out comparing Etonogestrel/Ethinylestradiol Leon Pharma with the reference product (further discussed in section IV.2).

Manufacturing process
The manufacturing process has been validated according to relevant European/ICH guidelines. Process validation data on the product have been presented for three batches in accordance with the relevant European guidelines.

Control of excipients
The MAH provided sufficient data for the use of polyurethane with an appropriate characterisation of the molecular weight range. The specifications for the skin polymer ethylene vinyl copolymer are also 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, mass of the ring, external diameter, thickness, tensile strength, two identification methods for etonogestrel and ethinyl estradiol, assay of etonogestrel and ethinylestradiol, content uniformity of etonogestrel and ethinyl estradiol, *in vitro* elution of etonogestrel and ethinylestradiol, related substances of etonogestrel and ethinylestradiol 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 three batches from the proposed production site have been provided, demonstrating compliance with the specification.

Stability of drug product
Three batches drug product have been put on stability at 2°C-8°C (24 months), 25°C/60% RH (24 months) and 40°C/75% RH (6 months). For the drug elution results no unusual results have been observed. On the basis of the data submitted, a shelf-life was granted of two years. The following storage condition applies: This medicinal product does not require any special temperature storage conditions. Store 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 Etonogestrel/Ethinylestradiol Leon 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 Toxicology

The MAH has provided a comprehensive risk assessment on possible extractables, leachables and impurities which could be present in the vaginal ring or be formed during use of the ring.

- Extractables are compounds that can be extracted from the container closure system when in the presence of a solvent. They are determined in laboratory experiments using neat solvents under conditions that predict the “Worst Case” conditions of exposure.
- Leachables are compounds that leach into the drug product formulation from the container closure as a result of direct contact with the formulation. They are determined in the presence of the drug or drug components during normal use.

For the extractables and leachables no compounds of concern were identified and therefore there is no concern for human health. For one specified impurity the shelf-life specification was tightened. In view of this, the MAH also tightened accordingly the shelf-life specification on total impurities.

III.2 Ecotoxicity/environmental risk assessment (ERA)

Since Etonogestrel/Ethinylestradiol Leon Pharma 0.120 mg/0.015 mg per 24 hours, vaginal delivery system 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.3 Discussion on the non-clinical aspects

This product is a generic formulation of NuvaRing 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 and pharmacokinetics data. An adequate risk assessment has been provided on extractables and leachables, showing no concerns for human health. The member states agreed that no further non-clinical studies are required.

IV. CLINICAL ASPECTS

IV.1 Introduction

Ethinylestradiol and etonogestrel are well-known active substances 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

Bioequivalence study
The MAH conducted a bioequivalence study in which the pharmacokinetic profile of the test product Etonogestrel/Ethinylestradiol Leon Pharma 0.120 mg/0.015 mg per 24 hours, vaginal delivery system (Laboratorios León Farma S.A, Spain) is compared with the pharmacokinetic profile of the reference product NuvaRing (Organon Ltd, Spain).

The choice of the reference product
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.

Design
A single centre, randomised, single dose, laboratory-blinded, two-period, two-sequence, crossover comparative bioequivalence study was carried out under fasted conditions in 40 healthy female subjects, aged 19-45 years. Each subject received a single dose (delivering 0.120 mg/0.015 mg per day) of one of the two ethinylestradiol/etonogestrel formulations. There were two dosing periods, separated by a washout period of 28 days.

Blood samples were collected over a period of 36 days, in which one sample was collected prior to insertion of the ring. 27 samples were collected before ring removal and nine samples were collected after removal of the ring. After collection of the 672-hour blood sample, the ring was removed and further blood samples were collected up to 840 hours (corresponding to up to 168 hours following ring removal).

The study design is acceptable and the sampling scheme is adequate to estimate pharmacokinetic parameters. The wash-out period is sufficient. The ring was worn in this study for 28 days, which is in accordance with the SmPC of the reference product. Additionally, after removal of the ring sampling continued seven days, which is sufficient to characterise the elimination phase adequately.

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.
$C_{max\ after\ day\ 1}$, AUC_{0-504}, AUC_{0-t} are accepted as the main pharmacokinetic parameters. In addition, the AUC_{0-672} is considered as important, since the NuvaRing can be worn for a maximum of 4 weeks and should therefore be included in the primary pharmacokinetic parameters.
According to the guideline on pharmacokinetic and clinical evaluation of modified-release dosage forms (EMA/CHMP/EWP/280/96, Cor. 1) the MAH has provided partial AUC's and the statistical evaluation of those partial AUC's. The choice of the time interval of these partial AUC's is sufficiently supported.

Results
A total of five subjects dropped out during this trial, of which four subjects withdrew consent for personal reasons (not related to clinical events) and one subject withdrew for safety reasons (investigator's decision). 33 subjects for ethinylestradiol and 35 subjects for etonogestrel were included in the final statistical analysis of AUC and C_{max}. For ethinylestradiol two subjects were excluded from the pharmacokinetic and statistical analysis due to a positive pre-dose ethinylestradiol concentration greater than 5% of C_{max} in period 1 and 2.

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

Treatment N=33	AUC_{0-t} pg.h/ml	$AUC_{0-\infty}$ pg.h/ml	AUC_{0-504} pg.h/ml	AUC_{0-672} pg.h/ml	C_{max} ng/ml	t_{max} h
Test	16440 ± 4806	16491 ± 4810	11809 ± 3368	15919 ± 4585	30.2 ± 7.6	360 (24 – 675)
Reference	14711 ± 4369	14764 ± 4382	10859 ± 3175	14284 ± 4204	27.0 ± 7.8	96 (24 – 672)
***Ratio (90% CI)**	1.13 (1.08 – 1.18)	--	1.10 (1.05 – 1.15)	--	1.13 (1.06 – 1.21)	--
CV (%)	8.4	--	8.5	--	13.4	--

$AUC_{0-\infty}$ 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 etonogestrel under fasted conditions.

Treatment N=35	AUC_{0-t} pg.h/ml	$AUC_{0-\infty}$ pg.h/ml	AUC_{0-504} pg.h/ml	AUC_{0-672} pg.h/ml	C_{max} ng/ml	t_{max} h
Test	1250 ± 399	1293 ± 392	867 ± 263	1180 ± 364	2.2 ± 0.65	360 (215 – 576)

Reference	1222 ± 444	1266 ± 440	858 ± 310	1154 ± 413	2.2 ± 0.9	312 (96 – 672)
***Ratio (90% CI)**	1.05 (1.00 – 1.09)	--	1.04 (0.99 – 1.09)	--	1.05 (0.97 – 1.13)	--
CV (%)	9.1	--	10.1	--	16.7	--

$AUC_{0-\infty}$ 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 Etonogestrel/Ethinylestradiol Leon Pharma is considered bioequivalent with NuvaRing.

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).

Temporary removal of the vaginal ring
The MAH has appropriately justified that the vaginal ring can be removed temporarily for a period of three hours without consequences for the release of the active substances and the contraceptive efficacy.

Pharmacokinetic analysis after removal of the vaginal ring
The MAH provided information about the concentration of active substances after the removal of the vaginal ring (up to three hours). The samples used for this analysis have been collected after 672 hours (immediately before vaginal ring removal) and 675 hours (+3 hours after vaginal ring removal).
The analysis of the removal of the vaginal ring was performed by means of the analysis of the concentration at time pre-removal, the concentration at time three hours after removal and $AUC_{672-675h}$.

As summarised in the tables below, the concentrations after 675 hours are similar (etonogestrel) or slightly higher (ethinylestradiol) in the case of test product. This reflects that the efficacy was not lost for test product after removal comparing with the NuvaRing. When evaluating the percentage of decrease in the first three hours after removal (as C_{672h}-C_{675h}/C_{672h}), the results are similar when comparing test vs reference in both, etonogestrel (14.63% vs 14.63%) and ethinylestradiol (11.84% vs 11.32%). These results are also confirmed when the analysis is based on $AUC_{672-675h}$. This also shows that the efficacy is not lost after removal (comparing with reference).

Table 3 Summary of Main Study Results of Etonogestrel, CEO-P9-825

Parameter (Units)	**Test**		**Reference**	
	Mean	**(C.V. %)**	**Mean**	**(C.V. %)**
$AUC_{672-675}$ (pg·h/ml)	5011.0	(35.7)	4803.0	(38.8)
ln (AUC672-675)	8.4511	(4.6)	8.3988	(5.0)
C_{672} (pg/ml)	1800.8	(33.9)	1727.8	(36.6)
ln (C672)	7.4358	(4.9)	7.3855	(5.3)
C_{675} (pg/ml)	1537.4	(38.3)	1474.9	(41.8)
ln (C_{675})	7.2579	(5.9)	7.2050	(6.3)

Table 4 Comparison of Results with Standard for Bioequivalence Etonogestrel, CEO-P9-825

Parameter	**Intra-Subject C.V. (%)**	**Geometric LSmeans[a]**		**Ratio (%)**	**94.12% Confidence Limits (%)**	
		Test	**Reference**		**Lower**	**Upper**
$AUC_{672-675}$	9.5	4729.0	4450.2	106.26	101.62	111.12
C_{672}	8.8	1710.4	1615.8	105.85	101.54	110.35
C_{675}	10.9	1436.5	1349.0	106.49	101.17	112.08

a units are pg/ml for C672 and C675; units are pg·h/mL for AUC672-C675

Table 5 Summary of Main Study Results of Ethinylestradiol, CEO-P9-825

Parameter (Units)	Test		Reference	
	Mean	(C.V. %)	Mean	(C.V. %)
$AUC_{672-675}$ (pg·h/ml)	66.70	(35.6)	56.01	(35.6)
ln ($AUC_{672-675}$)	4.1436	(8.2)	3.9724	(8.2)
C_{672} (pg/ml)	23.64	(35.7)	19.79	(35.3)
ln (C_{672})	3.1048	(11.1)	2.9320	(11.0)
C_{675} (pg/ml)	20.81	(36.3)	17.55	(36.6)
ln (C_{675})	2.9784	(11.3)	2.8106	(11.6)

Table 6 Comparison of Results with Standard for Bioequivalence Ethinylestradiol, CEO-P9-825

Parameter	Intra-Subject C.V. (%)	Geometric LSmeans [a]		Ratio (%)	94.12% Confidence Limits (%)	
		Test	Reference		Lower	Upper
$AUC_{672-675}$	12.4	63.31	52.93	119.63	112.61	127.08
C_{672}	12.4	22.36	18.71	119.52	112.52	126.96
C_{675}	12.8	19.79	16.56	119.49	112.28	127.16

The results of the bioequivalence study showed that three hours after the removal of the vaginal ring, the percentage of decrease in the concentrations of both etonogestrel and ethinylestradiol are equal for test and reference products. When comparing by means of a bioequivalence approach, the plasma levels remains at a higher level in the case of test product, assuring that the efficacy during the 3-hours removal will be at least similar to the reference product.
The elimination phase of ethinylestradiol and etonogestrel has been adequately characterised. The concentrations of etonogestrel and ethinylestradiol are in the therapeutic range three hours after removal of the ring, when the ring has been worn for four weeks.

Analysis of spontaneous expulsion during study
The data on spontaneous expulsion are considered very limited as the occurrence was low (two subjects) and the ring has been removed for only a very short period of time (one minute). The available pharmacokinetic data of women with ring expulsion are consistent with the mean pharmacokinetic data of the other subjects.

In-vitro analysis
An additional perspective was obtained from an *in vitro* analysis specifically designed to compare the effect of ring removal between the reference and test products, even in more stringent conditions than the described in the SmPC (with multiple ring removals in consecutive days).
Hence, in this study, rings were in elution for eight days. On days 4, 5 and 6, sub-group of rings were removed for one, two or three hours from the media. At the end of the removal time (1, 2 or 3 hours), the rings were put back on the elution media. Then, considering the three consecutive days, the rings were removed a total of three, six or nine hours during the eight days of experiment. An additional group of control rings was not removed from the media in the eight days of experiment.
The results show that both products have a similar profile and the release of etonogestrel and ethinylestradiol was not significantly affected by the removal up to three hours per day during three consecutive days.

Friendliness assessment
A friendliness study was included in the protocol of the bioequivalence study as a sub-study. Subjects completed a product questionnaire in which they provided their opinion using the 5-point scale. No clear differences were noted between the scores reported for the test and reference ring. 4% in each group reported expulsion, and indicated that it is easy to reinsert the ring. Based on the comparative data in this sub-study, it is concluded that the user friendliness of the test ring is comparable to that noted for the reference ring.

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 Etonogestrel/Ethinylestradiol Leon Pharma.

Summary table of safety concerns as approved in RMP:

Important identified risks	• Ring disconnection • Ring expulsion • Unintended pregnancies • Venous thromboembolic events (VTE) • Arterial thromboembolic events (ATE)
Important potential risks	• Toxic shock syndrome • Implant site fibrosis
Missing information	• Endometrial hyperplasia • Pelvic inflammatory disease

The Risk Minimisation Plan contains additional risk minimisation measures for the identified risks VTE and ATE. The MAH includes as additional risk minimisation measures a patient information card and a checklist for prescribers.

The implementation of the additional measures will be agreed at a national level in each of the member states.

IV.4 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the innovator product NuvaRing. 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 has (PL) 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 two 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 PL of medicinal products for human use.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Etonogestrel/Ethinylestradiol Leon Pharma 0.120 mg/0.015 mg per 24 hours, vaginal delivery system has a proven chemical-pharmaceutical quality and is a generic form of NuvaRing 0.120 mg/0.015 mg per 24 hour vaginal delivery system. NuvaRing 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 Etonogestrel/Ethinylestradiol Leon Pharma with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 18 May 2017.

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/3722/IA/001	Additional secondary packaging site	--	21-8-2017	Approval	
NL/H/3722/IA/002	Additional secondary packaging site	--	2-10-2017	Approval	