COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Levonorgestrel/Ethinylestradiol 0.15 mg/0.03 mg Focus, film-coated tablets

(levonorgestrel/ethinylestradiol)

NL Licence RVG 121002

Date: 3 July 2019

This module reflects the scientific discussion for the approval of Levonorgestrel/Ethinylestradiol Focus. The marketing authorisation was granted on 20 February 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

CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
EDQM	European Directorate for the Quality of Medicines
ERA	Environmental Risk Assessment
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 Medicines Evaluation Board (MEB) of the Netherlands has granted a marketing authorisation for Levonorgestrel/ Ethinylestradiol 0.15 mg/0.03 mg Focus, film-coated tablets from Focus Care Pharmaceuticals B.V.

The product is indicated for oral contraception.

A comprehensive description of the indications and posology is given in the SmPC.

This national procedure concerns a generic application claiming essential similarity with the innovator product Microgynon 30, 0.15 mg/0.03 mg, coated tablets (NL License RVG 08204) which has been registered in the Netherlands by Bayer B.V. since 5 September 1974.

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

II. QUALITY ASPECTS

II.1 Introduction

Levonorgestrel/Ethinylestradiol Focus 0.15 mg/0.03 mg Focus is a yellow, round tablet, with a diameter of 6 mm and thickness less than 4 mm approximately. Each film-coated tablet contains as active substance 0.15 mg of levonorgestrel and 0.03 mg of ethinylestradiol.

The film-coated tablets are packed in blisters of aluminium push-thru foil and PVC/PVDC film. The package contains 21 yellow tablets.

The excipients are:
Tablet core - lactose monohydrate, povidone K30 (E 1201), crospovidone type A (E 1202), magnesium stearate (E 470b)
Coating - partial hydrolysed polyvinyl alcohol (E 1203), titanium dioxide (E 171), macrogol 3350, talc (E 553b), iron oxide yellow (E 172)

II.2 Drug Substances

Levonorgestrel
The active substance levonorgestel is an established active substance described in the European Pharmacopoeia (Ph.Eur.). The active substance is a white to almost white

crystalline powder. Levonorgestrel is practically insoluble in water, sparingly soluble in methylene chloride and slightly soluble in ethanol.

The CEP procedure is used for the active substance levonorgestrel. 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 drug substance specification is fully in line with the currently valid Ph.Eur. monograph for levonorgestrel and the additional tests laid down in the CEP and includes additional requirements for residual solvents and for particle size. Batch analysis data demonstrating compliance with the drug substance specification was provided for three batches.

Stability of drug substance

The stability of the drug substance is not covered by the CEP. The MAH provided stability data of three commercial scale batches. The MAH applies the same or a more restrictive re-test period than the active substance manufacturer. The applied re-test period of the active substance manufacturer is four years. No storage conditions are needed.

Ethinylestradiol

The active substance ethinylestradiol is an established active substance described in the European Pharmacopoeia. The active substance is a white or slightly yellowish-white, crystalline powder. Ethinylestradiol is practically insoluble in water, freely soluble in alcohol. It dissolves in dilute alkaline solutions. The CEP procedure is used for both suppliers of this active substance.

Manufacturing process

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

Quality control of drug substance

The drug substance specification is in line with the currently valid Ph.Eur. monograph for ethinylestradiol and the additional tests laid down in the CEP and includes additional requirements for residual solvents and for particle size. Batch analysis data demonstrating compliance with the drug substance specification was provided for three batches.

Stability of drug substance

The stability data of the drug substance supplied by one supplier were assessed by the EDQM. According to the CEP, the active substance is stable for five years when stored in two polyethylene bags sealed inside a polyethylene container.

The MAH provided stability data of three commercial batches of the drug substance supplied by the second active substance manufacturer, supporting the claimed re-test period of four years. No specific storage conditions are needed.

II.3 Medicinal Product

Pharmaceutical development

The choice of excipients is justified and their functions explained. The pharmaceutical development of the product has been adequately described. The test and reference products used in the bioequivalence study are acceptable. The comparative dissolution data of the biobatches do not support bioequivalence as the reference product is sugar-coated and the test product is film-coated resulting in a lag time for the reference product. This is considered acceptable as bioequivalence has been demonstrated *in vivo*.

The acceptance criteria for routine dissolution testing of levonorgestrel and ethinylestradiol are in line with the Reflection paper on the dissolution specification for generic oral immediate release products.

Manufacturing process

The manufacturing process consists of blending, tableting and film-coating. The manufacturing process is considered to be a non-standard process due to the low content of active substances. The manufacturing process was sufficiently described. Process validation data were provided on three pilot-scale and three full-scale batches. All predefined acceptance criteria were met.

Control of excipients

With the exception of iron oxide yellow, all excipients comply with the Ph.Eur. Reference is made to the National Formulary with regard to iron oxide yellow. The provided specifications are acceptable.

Quality control of drug product

The product specification includes tests for appearance, identification of levonorgestrel, identification of ethinylestradiol, levonorgestrel assay, ethinylestradiol assay, levonorgestrel dissolution, ethinylestradiol dissolution, levonorgestrel content uniformity, ethinylestradiol content uniformity, levonorgestrel related substances, ethinylestradiol related substances and microbial control.

The release and end-of-shelf-life specifications differ with regard to the acceptance criteria for assay and related substances of both active substances which is justified based on the provided batch analysis and stability data. The drug product specification is acceptable.

In-house methods were adequately described and validated. Batch analysis data of three pilot-scale and three full-scale batches demonstrate compliance with the proposed release specification.

Stability of drug product

Stability data on the product has been provided on three pilot-scale batches stored at 25°C/60%RH (24 months), 30°C/70%RH (12 months) and 40°C/75%RH (six months) and three full-scale batches stored at 25°C/60%RH (24 months) and 40°C/75%RH (six months). The conditions used in the stability studies are according to the ICH stability guideline. A significant change in ethinylestradiol content was seen at accelerated storage conditions. The tablets are considered photostable based on results of photostability testing. The claimed shelf life of 24 months and storage condition ''Do not store above 30ºC“ are justified.

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

Scientific data and/or certificates of suitability issued by the EDQM have been provided and compliance with the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via medicinal products has been satisfactorily demonstrated. Lactose monohydrate comes from milk of healthy animals collected under the same conditions as milk suitable for human consumption. Magnesium stearate is of vegetable origin.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the MEB considers that Levonorgestrel/Ethinylestradiol 0.15 mg/0.03 mg Focus has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substances and finished product.
No post-approval commitments were made.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Levonorgestrel/Ethinylestradiol Focus 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 Microgynon 30, 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 MEB agreed that no further non-clinical studies are required.

III.3 Introduction

Levonorgestrel and ethinylestradiol 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 MEB agreed that no further clinical studies are required.

For this generic application, the MAH has submitted a bioequivalence study, which is discussed below.

III.4 Pharmacokinetics

The MAH conducted a bioequivalence study in which the pharmacokinetic profile of the test product Levonorgestrel/Ethinylestradiol 0.15 mg/0.03 mg Focus (Focus Care Pharmaceuticals B.V., the Netherlands) is compared with the pharmacokinetic profile of the reference product Microgynon 30 tablets (Bayer Schering Pharma AG, Germany).

The choice of the reference product in the bioequivalence study has been justified by comparison of dissolution results and compositions of reference products. 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 40 healthy female subjects, aged 22 - 43 years. Each subject received a single dose (0.15 mg/0.03 mg) of one of the 2 levonorgestrel/ethinylestradiol 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 pre-dose and at 0.25, 0.5, 0.75, 1, 1.25, 1.5, 1.75, 2, 2.5, 3, 4, 6, 8, 12, 16, 24, 36, 48 and 72 hours after administration of the products.

The overall study design is considered acceptable considering the absorption rate and half-lives. The study design is acceptable, considering the Tmax of 1 – 1.5 hours for both ethinylestradiol and levonorgestrel. The washout period of 28 days at least 10 times of elimination half-life for both ethinylestradiol and levonorgestrel is considered adequate (t1/2, 20 hours for ethinylestradiol and 20 hours for levonorgestrel according to the SmPC of Microgynon).

Both active substances may be taken without reference to food intake. From the literature it is known that food does not interact with the absorption of LNG and EE. 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
One subject did not complete the study due to personal reasons. Therefore a total of 39 subjects completed the study and were included in the pharmacokinetic and statistical analyses.

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

Treatment N=39	**AUC_{0-72} (pg.h/ml)**	**C_{max} (pg/ml)**	**t_{max} (h)**	**$t_{1/2}$ (h)**
Test	898 ± 369	79.9 ± 28.8	1.75 (1.0 – 4.0)	18.3 ± 4.0
Reference	886 ± 348	84.0 ± 31.4	1.75 (1.0 – 4.0)	18.3 ± 4.6
***Ratio (90% CI)**	1.0 (0.97 – 1.04)	0.95 (0.90 – 1.00)	--	--
CV (%)	8.8	12.3	--	--

AUC_{0-72} area under the plasma concentration-time curve from time zero to 72 hours
C_{max} maximum plasma concentration
t_{max} time for maximum concentration
$t_{1/2}$ half-life
CV coefficient of variation

**ln-transformed values*

Table 2. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, tmax (median, range)) of levonorgestrel under fasted conditions.

Treatment N=39	**AUC_{0-72} (pg.h/ml)**	**C_{max} (pg/ml)**	**t_{max} (h)**	**$t_{1/2}$ (h)**
Test	62547 ± 27170	4749 ± 1957	1.25 (0.75 – 4.0)	55 ± 22
Reference	60660 ± 26064	5055 ± 2059	1.25 (0.75 – 4.0)	59 ± 47
***Ratio**	1.03 (0.97 – 1.09)	0.94 (0.87 – 1.01)	--	--

(90% CI)				
CV (%)	14.6	19.7	--	--

AUC_{0-72} area under the plasma concentration-time curve from time zero to 72 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_{0-72} and C_{max} are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the submitted bioequivalence study Levonorgestrel/Ethinylestradiol 0.15 mg/0.03 mg Focus is considered bioequivalent with Microgynon 30 tablets.

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).

III.5 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 Levonorgestrel/Ethinylestradiol Focus.

Table 3. 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 • Disturbances of liver function • Pancreatitis • Increased blood pressure • Effect on hereditary angioedema
Important potential risks	• Worsening of endogenous depression/ depressed mood • Crohn's disease and ulcerative colitis
Missing information	---

The MEB agrees that routine pharmacovigilance activities and routine risk minimisation measures are sufficient for the risks and areas of missing information.

III.6 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the innovator product Microgynon. 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.

IV. USER CONSULTATION

The package leaflet (PL) has not been evaluated via a user consultation study. A bridging report was submitted with reference to the successfully user tested PL for a levonorgestrel/ ethinylestradiol product with 7 placebo tablets. The text is nearly the same and the layout of the daughter PL is similar to the parent PL. Differences between the texts have been highlighted and discussed in the report. Since the differences do not affect the key safety information, readability should not be affected and therefore no separate testing of the daughter PL is required.

V. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Levonorgestrel/Ethinylestradiol 0.15 mg/0.03 mg Focus, film-coated tablets has a proven chemical-pharmaceutical quality and is a generic form of Microgynon 30, 0.15 mg/0.03 mg, coated tablets. Microgynon 30 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.

The MEB, on the basis of the data submitted, considered that essential similarity has been demonstrated for Levonorgestrel/Ethinylestradiol Focus with the reference product, and have therefore granted a marketing authorisation. Levonorgestrel/Ethinylestradiol Focus was authorised in the Netherlands on 20 February 2018.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Scope	Type of modification	Product Information affected	Date of end of the procedure	Approval/ non approval	Summary/ Justification for refuse
Change in the name and/or address of the marketing authorisation holder	IA/G	Y	18-7-2018	Approval	N
Minor change in the manufacturing process of the finished product. Change in the batch size (including batch size ranges) of the finished product	IB/G	N	6-8-2018	Approval	N
Changes (Safety/Efficacy) to Human and Veterinary Medicinal Products: following assessment of the available date assessed by the PRAC signal in October 2018 recommendation for Hormonal Contraceptives	IA	Y	21-2-2019	Approval	N
Change in the name and/or address of a manufacturer/ importer of the finished product	IA	N	22-2-2019	Approval	N