IPAR

Public Assessment Report for a
Medicinal Product for Human Use

Scientific Discussion

Levonorgestrel/ Ethinylestradiol 150 micrograms/30 micrograms coated tablets
Levonorgestrel
Ethinylestradiol
PA22865/016/001

The Public Assessment Report reflects the scientific conclusion reached by the Health Products Regulatory Authority (HPRA) at the end of the evaluation process and provides a summary of the grounds for approval of a marketing authorisation for a specific medicinal product for human use. It is made available by the HPRA for information to the public, after deletion of commercially sensitive information. The legal basis for its creation and availability is contained in Article 21 of Directive 2001/83/EC, as amended. It is a concise document which highlights the main parts of the documentation submitted by the applicant and the scientific evaluation carried out by the HPRA leading to the approval of the medicinal product for marketing in Ireland.

CONTENTS

I. INTRODUCTION

II. QUALITY ASPECTS

III. NON-CLINICAL ASPECTS

IV. CLINICAL ASPECTS

V. OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

VI. REVISION DATE

VII. UPDATE

I. INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the HPRA has granted a marketing authorisation for Levonorgestrel/Ethinylestradiol 150 micrograms/30 micrograms coated tablets from Renata Pharmaceuticals (Ireland) Limited, on 21/08/20206 ,as an oral contraception. The decision to prescribe Levonorgestrel/ Ethinylestradiol should take into consideration the individual woman's current risk factors, particularly those for venous thromboembolism (VTE), and how the risk of VTE with Levonorgestrel/ Ethinylestradiol compares with other combined hormonal contraceptives (CHCs) (see sections 4.3 and 4.4).

This application for a marketing authorisation was submitted in accordance with Article 10.1 of Directive 2001/83/EC and is referred to as a Generic application, claiming essential similarity.

Each tablet contains Levonorgestrel 0.15 mg & Ethinylestradiol 0.03 mg. The tablets of the applicant's product Levonorgestrel/Ethinylestradiol 150 microgram/ 30 microgram coated tablets are of the same indication, strength, and route of administration as that of the reference medicinal product Microgynon 30 - 0.15 mg / 0,03 mg, comprimés enrobés.

The active substances, Levonorgestrel/Ethinylestradiol, are not considered a new active substance. The applicant did not seek scientific advice. The product is subject to prescription which may be renewed.

The HPRA was the reference member state (RMS) and Belgium was the only concerned member state (CMS).

The Summary of Product Characteristics for (SmPC) for this medicinal product is available on the HPRA's website at www.hpra.ie

Name of the product	Levonorgestrel/Ethinylestradiol 150 microgram / 30 microgram coated tablets.
Name(s) of the active substance(s) (INN)	Levonorgestrel, Ethinylestradiol
Pharmacotherapeutic classification (ATC code)	G03AA07
Pharmaceutical form and strength(s)	150 microgram / 30 microgram coated tablets.
Marketing Authorisation Number(s) in Ireland (PA)	PA22865/016/001
Marketing Authorisation Holder	Renata Pharmaceuticals (Ireland) Limited
MRP/DCP No.	IE/H/1283/001/DC
Reference Member State	IE
Concerned Member State	BE

II. QUALITY ASPECTS

II.1. Introduction

This application is for Levonorgestrel/ Ethinylestradiol 150 micrograms/ 30 micrograms coated tablets.

II.2 Drug substance

The active substances are levonorgestrel and ethinylestradiol which are established active substances both described in the European Pharmacopoeia, and are manufactured in accordance with the principles of Good Manufacturing Practice (GMP)

The active substance specifications are considered adequate to control the quality and meets current pharmacopoeial requirements. Batch analytical data demonstrating compliance with this specification has been provided.

II.3 Medicinal product

P.1 Composition

The excipients in the medicinal product are listed in section 6.1 of the SmPC.
A visual description of the product is included in section 3 of the SmPC.

P.2 Pharmaceutical Development

The product is an established pharmaceutical form, and its development is adequately described in accordance with the relevant European guidelines.

P.3 Manufacture of the Product

The product is manufactured in accordance with the principles of good manufacturing practice (GMP) at suitably qualified manufacturing sites.

The manufacturing process has been validated according to relevant European/ICH guidelines, and the process is considered to be sufficiently validated.

P.4 Control of Other Substances (Excipients/*Ancillary Substances*)

All ingredients comply with Ph. Eur. or are adequately controlled by the manufacturer's specifications.

P.5 Control of Finished Product

The Finished Product Specification is based on the pharmacopoeial monograph for tablet dosage form, and the tests and control limits are considered appropriate for this type of product.

The analytical methods used are described in sufficient detail and are supported by validation data.

Batch analytical data for a number of batches from the proposed production site(s) have been provided and demonstrate the ability of the manufacturer to produce batches of finished product of consistent quality.

P.6 Packaging material

The approved packaging for this product is described in section 6.5 of the SmPC.

Evidence has been provided that the packaging complies with Ph. Eur./EU legislation for use with foodstuffs requirements.

P.7 Stability of the Finished Product

Stability data on the finished product in the proposed packaging have been provided in accordance with EU guidelines and support the shelf-life and storage conditions listed in sections 6.3 and 6.4 of the SmPC.

II.4 Discussion on Chemical, Pharmaceutical and Biological Aspects

The important quality characteristics of the product are well-defined and controlled. Satisfactory chemical and pharmaceutical documentation has been provided, assuring consistent quality of Levonorgestrel/ Ethinylestradiol 150 micrograms/ 30 micrograms coated tablets.

III. NON-CLINICAL ASPECTS

III.1 Introduction

This active substance is a generic formulation of Microgynon on the European market. As the pharmacodynamic, pharmacokinetic and toxicological properties of Levonorgestrel/Ethinylestradiol are well known, the applicant has not provided additional studies, and further studies are not required. The overview provided based on literature review is thus appropriate.

III.2 Pharmacology

N/A

III.3 Pharmacokinetics

N/A

III.4 Toxicology

N/A

III.5 Ecotoxicity/environmental risk assessment

This application was submitted prior to the implementation of the updated Guideline on the environmental risk assessment of medicinal products for human use (EMEA/CHMP/SWP/4447/00 Rev. 1-Corr.*) and therefore additional environmental risk studies were not requested as Levonorgestrel/Ethinylestradiol 150 microgram/30 microgram coated tablets is not expected to increase environmental exposure to the active substances.

III.6 Discussion on the non-clinical aspects

Pharmacodynamic, pharmacokinetic and toxicological properties of Levonorgestrel/Ethinylestradiol are well known since it has been marketed for several decades and resulting clinical experience is extensive. As Levonorgestrel/Ethinylestradiol are widely used, well-known active substances, the applicant has not provided additional studies, and further studies are not required. The nonclinical overview on the nonclinical pharmacology, pharmacokinetics and toxicology provided is adequate.

IV. CLINICAL ASPECTS

IV.1 Introduction

Both Levonorgestrel and Ethinylestradiol are well known active substance with established efficacy and tolerability.

The content of the SmPC approved during the decentralised procedure is in accordance with that accepted for the reference product Microgynon 30 - 0.15 mg / 0,03 mg, comprimés enrobés marketed by MAH.

For this generic application, the applicant has submitted a single (Study 0020-18) bioequivalence study in which the pharmacokinetic profile of the test product is compared with the pharmacokinetic profile of the reference product. An open label, balanced, randomized, single-dose, two-treatment, two-sequence, two-period, crossover oral bioequivalence study was carried out. Levonorgestrel/ Ethinylestradiol 150 micrograms/ 30 micrograms coated tablets, Renata Pharmaceuticals (Ireland) Limited, was compared to the reference product Microgynon® 30 coated tablets, Bayer PLC.
Based on the pharmacokinetic parameters of active substance, the reference tablet Microgynon® 30 coated tablets, marketed by Bayer PLC and test tablet Levonorgestrel/ Ethinylestradiol 150 micrograms/ 30 micrograms coated tablets, Renata Pharmaceuticals (Ireland) Limited are bioequivalent with extent to the rate and extent of absorption and fulfil the bioequivalence requirements outlined in the relevant CHMP Note for Guidance.

The content of the SmPC approved during the decentralised procedure is in accordance with that accepted for the reference product Microgynon® 30 coated tablets marketed by Bayer PLC.

The HPRA has been assured that GCP standards were followed in an appropriate manner in the studies conducted.

IV.2 Pharmacokinetics

Levonorgestrel

Absorption
Orally administered levonorgestrel is rapidly and completely absorbed. Peak serum concentrations of approximately 3-4 ng/mL are reached approximately 1 hour after a single dose. The bioavailability of levonorgestrel is almost complete after oral administration.

Distribution
Levonorgestrel is bound to serum albumin and to SHBG (sex hormone binding globulin). Only 1.3% of the total serum levonorgestrel concentration is present as the free steroid, about 64% is specifically bound to SHBG and about 35% is not specifically bound to albumin. The ethinyl estradiol-induced increase in SHBG influences the distribution of levonorgestrel which is bound to serum proteins and induces an increase in the fraction bound to SHBG and a decrease in the fraction bound to albumin. The apparent volume of distribution of levonorgestrel is approximately 184 L after single administration.

Biotransformation

Levonorgestrel is largely metabolised. The main metabolites in plasma are the conjugated and unconjugated forms of 3α, 5β-tetrahydrolevonorgestrel. *In vitro* and *in vivo* studies show that CYP3A4 is the main enzyme involved in the metabolism of levonorgestrel. The metabolic elimination rate for serum is approximately 1.3 to 1.6 mL/min/kg.

Elimination
Serum levonorgestrel levels decline in 2 phases. The terminal excretion phase is characterised by a half-life of approximately 20-23 hours. Levonorgestrel is not eliminated unchanged. Its metabolites are excreted in a urinary to biliary ratio of approximately 1:1. The elimination half-life of the metabolites is approximately 1 day.

Steady state
After daily administration, serum drug levels increase by a factor of 3 to 4 and reach steady-state concentration during the second half of a treatment cycle. The pharmacokinetic properties of levonorgestrel are influenced by SHBG levels which increase by a factor of 1.7 after daily administration of Levonorgestrel/Ethinylestradiol *per os*. This effect induces a decrease in the elimination rate to about 0.7 mL/min/kg at steady state.

Ethinylestradiol

Absorption
Orally administered ethinylestradiol is rapidly and completely absorbed. Serum peaks of approximately 95 pg/mL are reached after 1-2 hours. During absorption and the first hepatic pass, ethinylestradiol is extensively metabolised, which results in an average bioavailability of approximately 45% with a large interindividual variability of approximately 20 to 65%.

Distribution
Ethinylestradiol is highly but not specifically bound to serum albumin (approximately 98%) and induces increased serum concentrations of SHBG. An apparent distribution volume of approximately 2.8-8.6 L/kg has been determined.

Biotransformation
Ethinylestradiol undergoes pre-systemic conjugation, both in the mucosa of the small intestine and in the liver. Ethinylestradiol is primarily metabolised by aromatic hydroxylation, but a wide variety of hydroxylated and methylated metabolites are formed, and these metabolites are present as free metabolites and glucuronide/sulphate conjugates. The reported metabolic elimination rate is 2.3-7 mL/min/kg.

Elimination
Serum ethinylestradiol levels decline in 2 phases of distribution, characterised by half-lives of approximately 1 hour and 10-20 hours, respectively. Unchanged ethinyl estradiol is not eliminated; ethinylestradiol metabolites are eliminated in a urinary to biliary ratio of 4:6. The elimination half-life of the metabolites is approximately 1 day.

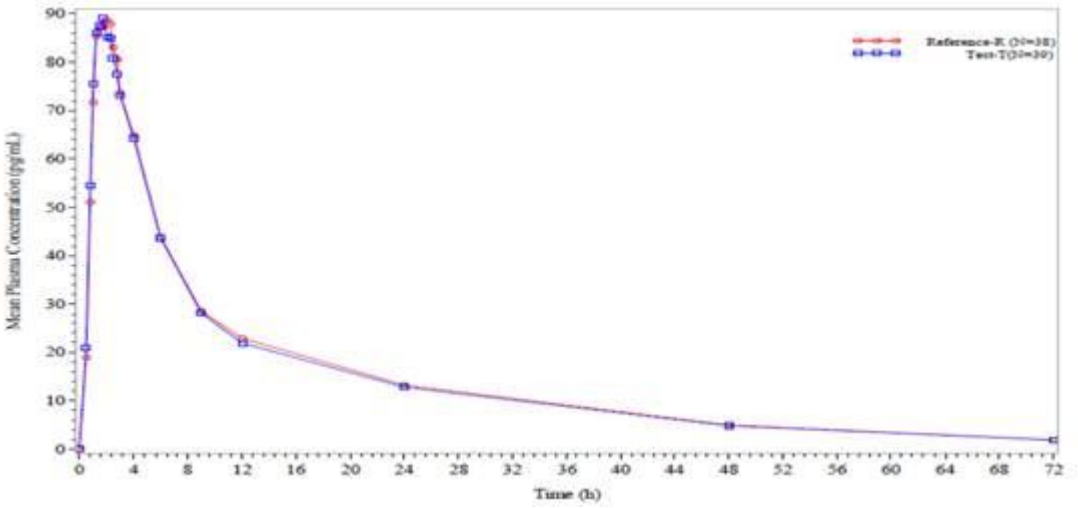
Steady state
Serum ethinylestradiol concentrations increase slightly after daily oral administration of Levonorgestrel/Ethinylestradiol. Peak concentrations at the end of a treatment cycle are approximately 114 pg/mL. Due to the variable half-life of the terminal serum distribution phase and daily intake, steady-state serum concentrations are reached after approximately one week.

IV.3 Pharmacodynamics

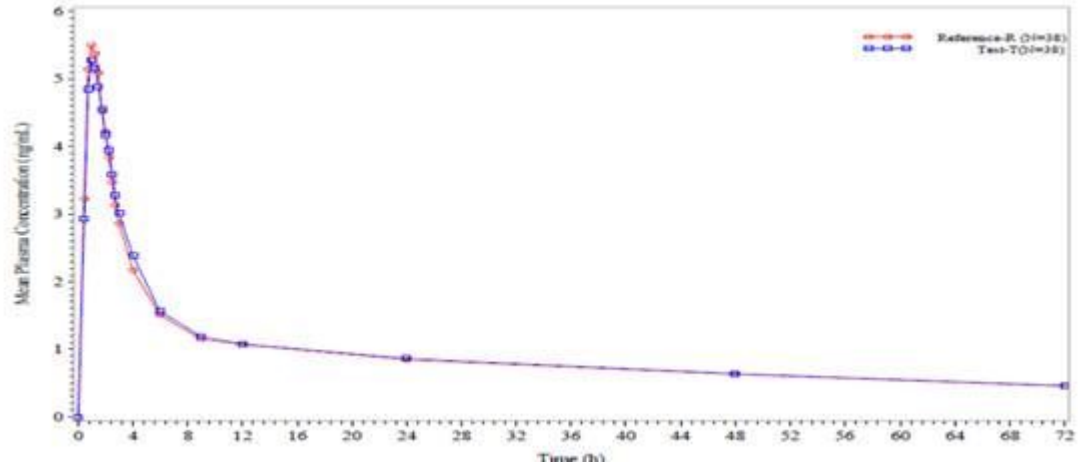
No new pharmacodynamic data were submitted and none are required for an application of this type.

IV.4 Clinical Efficacy

Mean plasma concentration vs. time curve for Ethinylestradiol



Mean plasma concentration vs. time curve for Levonorgestrel



Based on the submitted bioequivalence study Levonorgestrel 0.15 mg and Ethinylestradiol 0.03 mg Sugar Coated Tablets can be considered bioequivalent with Microgynon® 30 (Levonorgestrel 0.15 mg and Ethinylestradiol 0.03 mg) Sugar Coated Tablets.

No new efficacy data were submitted and none are required for an application of this type.

IV.5 Clinical Safety

The test and reference products were tolerated by the subjects.

No new safety data were submitted, and none are required for an application of this type.

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 150 micrograms/30 micrograms coated tablets.

Safety specification

Summary of safety concerns	
Important identified risks	None
Important potential risks	None
Missing information	None

Pharmacovigilance Plan
Routine pharmacovigilance is suggested and no additional pharmacovigilance activities are proposed by the applicant, which is endorsed.

Risk minimisation measures

Routine risk minimisation is suggested and no additional risk minimisation activities are proposed by the applicant, which is endorsed.

Summary of the RMP
The submitted Risk Management Plan, version 0.1 signed 16th March 2023 is considered acceptable.

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:
- At the request of the RMS;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time, but via different procedures.

Periodic Safety Update Report (PSUR)

With regard to PSUR submission, the MAH should take the following into account:

- PSURs shall be submitted in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal. Marketing authorisation holders shall continuously check the European medicines web-portal for the DLP and frequency of submission of the next PSUR.
- For medicinal products authorized under the legal basis of Article 10(1) or Article 10a of Directive 2001/83/EC, no routine PSURs need to be submitted, unless otherwise specified in the EURD list.
- In case the active substance will be removed in the future from the EURD list because the MAs have been withdrawn in all but one MS, the MAH shall contact that MS and propose DLP and frequency for further PSUR submissions together with a justification

IV.6 Discussion on the clinical aspects

This application concerns a generic medicinal product Levonorgestrel/ Ethinylestradiol 150 micrograms/ 30 micrograms coated tablets referencing Microgynon 30 0,15 mg / 0,03 mg, comprimés enrobés developed by BAYER SA NV, (License Number: BE091235), and which have been authorised in Belgium since 1/10/1974. Bioequivalence with the reference medicinal product has been demonstrated. No clinically relevant differences in efficacy or safety are anticipated in the proposed indication. The benefit–risk balance is favourable.

V. OVERALL CONCLUSIONS

Levonorgestrel/ Ethinylestradiol 150 micrograms/ 30 micrograms coated tablets is a generic form of Microgynon 30 0,15 mg / 0,03 mg, comprimés enrobés which is a well-known medicinal product with a proven chemical-pharmaceutical quality and an established favourable efficacy and safety profile.

Bioequivalence has been shown to be in compliance with the CHMP guidance documents. The SmPC is consistent with that of the reference product.

The MAH has provided written confirmation that systems and services are in place to ensure compliance with their pharmacovigilance obligations.

The HPRA, on the basis of the data submitted considered that Levonorgestrel/ Ethinylestradiol 150 micrograms/ 30 micrograms coated tablets demonstrated bioequivalence with the reference product as well as a satisfactory risk/benefit profile and therefore granted a marketing authorisation.

VI. REVISION DATE

20.08.2031