Public Assessment Report

Scientific discussion

Leanova 0.15 mg/0.03 mg, coated tablets
(levonorgestrel/ethinylestradiol)

NL/H/3148/001/DC

Date: 19 September 2016

This module reflects the scientific discussion for the approval of Leanova 0.15 mg/0.03 mg, coated tablets. The procedure was finalised on 16 March 2015. For information on changes after this date please refer to the ‘steps taken after finalisation’ at the end of this PAR.
**List of abbreviations**

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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</thead>
<tbody>
<tr>
<td>ASMF</td>
<td>Active Substance Master File</td>
</tr>
<tr>
<td>CEP</td>
<td>Certificate of Suitability to the monographs of the European Pharmacopoeia</td>
</tr>
<tr>
<td>CHMP</td>
<td>Committee for Medicinal Products for Human Use</td>
</tr>
<tr>
<td>CMD(h)</td>
<td>Coordination group for Mutual recognition and Decentralised procedure for human medicinal products</td>
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<tr>
<td>CMS</td>
<td>Concerned Member State</td>
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<tr>
<td>EDMF</td>
<td>European Drug Master File</td>
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<td>EDQM</td>
<td>European Directorate for the Quality of Medicines</td>
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<td>EEA</td>
<td>European Economic Area</td>
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<tr>
<td>ERA</td>
<td>Environmental Risk Assessment</td>
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<tr>
<td>ICH</td>
<td>International Conference of Harmonisation</td>
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<tr>
<td>MAH</td>
<td>Marketing Authorisation Holder</td>
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<td>Ph.Eur.</td>
<td>European Pharmacopoeia</td>
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<td>PL</td>
<td>Package Leaflet</td>
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<tr>
<td>RH</td>
<td>Relative Humidity</td>
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<tr>
<td>RMP</td>
<td>Risk Management Plan</td>
</tr>
<tr>
<td>SmPC</td>
<td>Summary of Product Characteristics</td>
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<tr>
<td>TSE</td>
<td>Transmissible Spongiform Encephalopathy</td>
</tr>
</tbody>
</table>
I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Leanova 0.15 mg/0.03 mg, coated tablets from Stada Arzneimittel AG.

The product is indicated for oral contraception. 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 Microgynon 30, 0.15 mg/0.03 mg coated tablets (NL License RVG 08204) which has been registered in the Netherlands by Schering Nederland BV (currently Bayer B.V.) since 25 September 1974 (original product).

The concerned member state (CMS) involved in this procedure was Czech Republic.

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

II. QUALITY ASPECTS

II.1 Introduction

Leanova 0.15 mg/0.03 mg is a white circular, biconvex, sugarcoated tablet and contains 150 micrograms levonorgestrel and 30 micrograms ethinylestradiol.

The tablets are packed in PVC-PVdC/Aluminum blisters.

The excipients are:

- **tablet core** - lactose monohydrate, maize starch, talc, povidone K-25, magnesium stearate
- **coating** - sucrose, talc, calcium carbonate, povidone K-90, glycerol, macrogol 6000, titanium dioxide (E171), carnauba wax.

II.2 Drug Substances

*Levonorgestrel*

The active substance levonorgestrel is an established active substance described in the European Pharmacopoeia (Ph.Eur.). It is a white or almost white crystalline powder, which is practically insoluble in water, sparingly soluble in methylene chloride and slightly soluble in ethanol. No polymorphism is described for levonorgestrel.

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 European Pharmacopoeia.

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 in accordance with the Ph.Eur. monograph on levonorgestrel and the CEP. Additional specifications have been laid down by the MAH. Batch analytical data demonstrating compliance with the specification have been provided for five batches.
Stability of drug substance
The active substance is stable for 60 months 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 an established active substance described in the European Pharmacopoeia. It is a white to faintly yellowish white crystalline powder, which is freely soluble in ether, ethanol, acetone and dioxane, soluble in alkali hydroxide solutions, sparingly soluble in chloroform and practically insoluble in water. Ethinylestradiol exhibits polymorphism, two polymorphic forms of ethinylestradiol are known, i.e. an anhydrate and a solvate. The drug substance used corresponds to the anhydrate.

The CEP procedure is also used for 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 active substance specification is in accordance with the Ph.Eur. monograph on ethinylestradiol and the additional CEP specifications. Batch analytical data demonstrating compliance with the specification have been provided for two batches.

Stability of drug substance
The active substance is stable for 36 months when stored under the stated conditions. Assessment thereof was part of granting the CEP and has been granted by the EDQM.

II.3 Medicinal Product

Pharmaceutical development
The development of the product has been described, the choice of excipients is justified and their functions explained. The main development studies concern the characterisation of the reference product, development of lactose granules, optimization of the tablet core composition to achieve good blend uniformity and optimization of the tablet composition to achieve comparable dissolution profiles to the reference product. A bioequivalence study has been performed versus the reference medicinal product. The test batch used in the bioequivalence study was manufactured according to the finalized composition and manufacturing process. The pharmaceutical development of the product has been adequately performed.

Dissolution of a test batch and two commercial batches of the drug product showed similar dissolution profiles (f2>50) for both active substances.

Manufacturing process
The main steps of the manufacturing process are the preparation of the lactose granules by wet granulation, pre-mixing, blending and lubrication, compression and the preparation and application of the coating. Finally the tablets are polished with carnauba wax and packed in blisters. The manufacturing process is considered a non-standard process given the low content of the active ingredients. The manufacturing process has been adequately validated according to relevant European guidelines. Process validation data on the product has been presented for six pilot scaled batches and three full scaled batches.

Control of excipients
Except for purified water, all excipients comply and are tested in accordance with their Ph. Eur. monographs. Purified water complies and is tested according to the British Pharmacopoeia monograph, but harmonized with the Ph. Eur. monograph. These specifications are acceptable.

Quality control of drug product
The product specification includes tests for description, identification, average weight, thickness, diameter, disintegration, dissolution, uniformity of content, assay, related substances and microbial quality. Except for average weight, dissolution and related substances, the release and shelf-life requirements are identical. The specification is acceptable. The analytical methods have been adequately described and validated. Batch analytical data from the proposed production site have
been provided on six pilot scaled and three full scaled batches, demonstrating compliance with the release specification.

**Stability of drug product**

Stability data on the product have been provided. Three pilot scaled batches were stored at 25°C/60% RH (36 months) and 40°C/75% RH (6 months). The conditions used in the stability studies are according to the ICH stability guideline. The batches were stored in PVC-PVdC/Al-blister. At both storage conditions a slight increase in impurities was seen. It was demonstrated that the drug product is not sensitive to light exposure. The proposed shelf-life of 36 months without any special storage requirements is justified.

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

Lactose monohydrate is the only material of animal origin used in the manufacture of the drug product. 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.

**II.4 Discussion on chemical, pharmaceutical and biological aspects**

Based on the submitted dossier, the member states consider that Leanova 0.15 mg/0.03 mg, coated tablets 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 Leanova 0.15 mg/0.03 mg 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 member states agreed that no further non-clinical studies are required.

**IV. CLINICAL ASPECTS**

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 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.1 Pharmacokinetics**

For this generic application, the MAH has submitted a bioequivalence study in which the pharmacokinetic profile of the test product Leanova 0.15 mg/0.03 mg (Stada Arzneimittel AG, DE) is
compared with the pharmacokinetic profile of the reference product Microgynon 30, 0.15 mg/0.03 mg coated tablets (Bayer B.V., NL).

The choice of the reference product in the bioequivalence study has been justified by comparison of dissolution results and compositions of reference products 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 30 healthy female subjects, aged 18-40 years. Each subject received a single dose (2 x 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 31 days.

Blood samples were collected pre-dose and at 0.25, 0.50, 0.75, 1.00, 1.25, 1.50, 1.75, 2.00, 2.25, 2.50, 3.00, 3.5, 4.00, 5.00, 6.00, 8.00, 10.00, 12.00, 24.00, 48.00, 72.00, 96.00, 120.00, 144.00 and 168.00 hours after administration of the products.

This study design is acceptable. Blood collection time till 168 hours was sufficient, covering more than 5 half-lives of levonorgestrel based on a t½ of 30 hours and 11 half-lives of ethinylestradiol based on a t½ of 15 hours. Levonorgestrel and ethinylestradiol may be taken without reference to food intake. From the literature it is known that food does not interact with the absorption of levonorgestrel and ethinylestradiol. Therefore, a food interaction study is not deemed necessary.

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 was withdrawn from the study due to an adverse event in period 2. Twenty-nine subjects completed both periods and were eligible for pharmacokinetic analysis.

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

<table>
<thead>
<tr>
<th>Treatment</th>
<th>N=29</th>
<th>AUC₀-₄</th>
<th>AUC₀-∞</th>
<th>C max</th>
<th>t max</th>
<th>t₁/₂</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>ng.h/ml</td>
<td>ng.h/ml</td>
<td>ng/ml</td>
<td>h</td>
<td>h</td>
</tr>
<tr>
<td>Test</td>
<td>205 ± 282</td>
<td>273 ± 530</td>
<td>10.51 ± 4.29</td>
<td>1.71 ± 0.53</td>
<td>--</td>
<td></td>
</tr>
<tr>
<td>Reference</td>
<td>209 ± 291</td>
<td>379 ± 1062</td>
<td>12.51 ± 5.61</td>
<td>1.25 ± 0.30</td>
<td>--</td>
<td></td>
</tr>
<tr>
<td>*Ratio (90% CI)</td>
<td>1.00 (0.92-1.08)</td>
<td>0.96 (0.89-1.03)</td>
<td>0.86 (0.81-0.91)</td>
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<tr>
<td>CV (%)</td>
<td>140</td>
<td>282</td>
<td>45</td>
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</tr>
</tbody>
</table>

*AUC₀-₄ area under the plasma concentration-time curve from time zero to t hours
*AUC₀-∞ area under the plasma concentration-time curve from time zero to infinity
*C max maximum plasma concentration
*t max time for maximum concentration
*t₁/₂ half-life
*CV coefficient of variation

Table 2. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t max (median, range)) of ethinylestradiol under fasted conditions.
### Conclusion on bioequivalence study

The 90% confidence intervals calculated for \( \text{AUC}_{0-t} \), \( \text{AUC}_{0-\infty} \) and \( \text{C}_{\text{max}} \) are in agreement with those calculated by the MAH and are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the pharmacokinetic parameters of levonorgestrel and ethinylestradiol under fasted conditions, it can be concluded that Leanova 0.15 mg/0.03 mg and Microgynon 30 tablets are bioequivalent with respect to rate and extent of absorption, and fulfil the bioequivalence requirements outlined in the relevant CHMP Note for Guidance.

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.2 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 Leanova 0.15 mg/0.03 mg, coated tablets.

- **Summary table of safety concerns as approved in RMP**

<table>
<thead>
<tr>
<th>Important identified risks</th>
<th>Venous thromboembolism</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Arterial thromboembolism</td>
</tr>
<tr>
<td></td>
<td>Benign and malign liver tumours</td>
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<tr>
<td>Breast cancer</td>
<td>Cervical cancer</td>
</tr>
<tr>
<td>Disturbance of liver function</td>
<td>Pancreatitis</td>
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<tr>
<td>Increased blood pressure</td>
<td>Effect on hereditary angioedema</td>
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</tbody>
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<table>
<thead>
<tr>
<th>Important potential risks</th>
<th>Worsening of endogenous depression</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Worsening of Crohn’s disease and ulcerative colitis</td>
</tr>
</tbody>
</table>

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.3 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the innovator product Microgynon 30, 0.15 mg/0.03 mg coated tablets. 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

A user consultation with target patient groups on the package leaflet (PL) has been performed on the basis of a bridging report. For the content, reference was made to an approved product with the same active ingredients. Furthermore, the applicant refers to an already positive finalised procedure with the same composition of the tablets and indication. In this procedure the same applicant is involved. For the layout, the applicant referred to the fact that there are many PLs which were user-tested and proven readable in the applicant’s layout. This is acceptable. Overall, the bridging report submitted by the applicant has been found acceptable.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION.

Leanova 0.15 mg/0.03 mg, 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.

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 Leanova 0.15 mg/0.03 mg, with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 16 March 2015.
## STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

<table>
<thead>
<tr>
<th>Scope</th>
<th>Procedure number</th>
<th>Type of modification</th>
<th>Date of start of the procedure</th>
<th>Date of end of the procedure</th>
<th>Approval/ non approval</th>
<th>Assessment report attached</th>
</tr>
</thead>
<tbody>
<tr>
<td>Change in the name and/or address of a manufacturer/importer of the finished product (including batch release or quality control testing sites); the activities for which the manufacturer/importer is responsible do not include batch release</td>
<td>NL/H/3148/I A/001</td>
<td>IA</td>
<td>24-12-2015</td>
<td>21-01-2016</td>
<td>Approval</td>
<td>N</td>
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</tbody>
</table>