This part outlines the scientific assessment and knowledge about this product at the time of prequalification. Updates to this information are included in parts 1 to 5 and 8 of this WHOPAR.

# SCIENTIFIC DISCUSSION

| | |
|---|---|
| **Name of the Finished Pharmaceutical Product** | [RH071 trade name]* |
| **Manufacturer of Prequalified Product** | Laboratorios Leon Farma SA |
| **Active Pharmaceutical Ingredient(s) (API)** | Ethinylestradiol / levonorgestrel |
| **Pharmaco-therapeutic group (ATC Code)** | Progestogens and oestrogens, fixed combinations (G03AA07) |
| **Therapeutic indication** | [RH071 trade name] is an oral combined hormonal contraceptive (CHC) agent for women. |

## 1. Introduction

[RH071 trade name] is an oral combined hormonal contraceptive (CHC) agent for women.

## 2. Assessment of quality

The assessment was done in accordance with the requirements of WHO's *Guidelines on submission of documentation for a multisource (generic) finished pharmaceutical product for the WHO Prequalification of Medicines Programme: quality part*.

### Active pharmaceutical Ingredient (API)

CEPs (Certificates of Suitability) issued by the EDQM were submitted, ensuring good manufacturing control and applicability of the Ph.Eur monographs to control quality of the APIs.

The FPP manufacturer's API specifications include particle size distribution which is regarded a critical quality attribute of ethinylestradiol and levonorgestrel. The acceptance criteria for this parameter was derived from the information of the API lots used in the FPP biobatch.

Stability testing was conducted according to the requirements of WHO. The proposed re-test periods is justified based on the stability results when the APIs is stored in the original packaging.

### Other ingredients

Other ingredients used in the core tablet formulation include lactose monohydrate, povidone, crospovidone and magnesium stearate, all being pharmacopoeial controlled. The commercially sourced proprietary film-coating mixture contains polyvinyl alcohol, titanium dioxide, macrogol, talc and iron oxide yellow which are controlled by acceptable specifications. BSE/TSE compliance declarations were provided for all the excipients.

* Trade names are not prequalified by WHO. This is the national medicines regulatory authority's responsibility.

**Finished pharmaceutical product (FPP)**

*Pharmaceutical development and manufacture*

The multisource product consists of a yellow, round, biconvex film-coated tablet, plain on both sides (active tablet) and a white, round, film-coated tablet, plain on both sides (placebo tablet). The tablets are packaged in a PVC/PVDC-aluminium blister card. Each blister card contains 21 active tablets (yellow) plus 7 placebo tablets (white).

The formulation development of the multisource product was partially based on ethinylestradiol/levonorgestrel 0.02 mg /0.10 mg sugar-coated tablets which is currently approved and marketed in the European Union.

The aim of the formulation development was to develop a product bioequivalent to the comparator product, Mycrogynon®, and feasible to be manufactured. The study of the excipients of the comparator product suggested wet granulation as the most probable manufacturing method. However as per the above ethinylestradiol/levonorgestrel 0.02 mg /0.10 mg sugar-coated tablets, direct compression manufacturing methods were used to simplify the process. Regarding ethinylestradiol/levonorgestrel 0.03 mg/ 0.15 mg film-coated tablets, it was concluded that a key point of the method of the manufacture was the use of micronized levonorgestrel and the inclusion of a disintegrant in the formulation. For this very low dose, high potency product, critical issues regarding blend and content uniformity were addressed via the control strategy of the manufacturer. Various experiments were performed to select and optimize the concentration of excipients and other process parameters to obtain tablets of desired characteristics. Satisfactory in-process controls have been established.

*Specifications*

The finished product specifications of the active tablet include tests for appearance, identification of the APIs (HPLC and UV), assay (HPLC), water content, dissolution (HPLC detection), content uniformity (uniformity of dosage units) related substances (HPLC) and microbial limits.

The finished product specifications of the placebo tablet include tests for appearance, average weight, disintegration time, identification of the APIs (absence of the APIs) and microbial limits.

*Stability testing*

Stability studies have been conducted at 30°C/75%RH as long-term storage condition and for six months at accelerated conditions in the packaging intended for marketing of the product. The data provided show that the product is stable at these storage conditions. Based on the available stability data, the proposed shelf life and storage conditions as stated in the SmPC are acceptable.

**Conclusion**

The quality part of the dossier is accepted.

## 3. Assessment of bioequivalence

The following bioequivalence study has been performed in 2015 according to internationally accepted guidelines.

A single-dose, comparative bioavailability study of two formulations of Levonorgestrel/EthinylEstradiol 0.15 mg/0.03 mg tablets under fasting conditions (study no. 2015-3826).

The objective of the study was to compare the bioavailability of the stated Levonorgestrel/Ethinyl-estradiol 0.15/0.03 mg FDC tablet manufactured by/for Laboratorios León Farma, Spain (test drug) with the reference formulation Microgynon ® (Bayer Schering Pharma AG) and to assess

bioequivalence. The comparison was performed as a single centre, open label, randomized, crossover study in healthy subjects under fasting conditions. Each subject was assigned to receive each of the following two treatments in a randomized fashion:

Treatment T: Test – 1 tablet Levonorgestrel/Ethinyl-Estradiol 0.15 mg/0.03 mg (levonorgestrel 0.15 mg + ethinylestradiol 0.03 mg) Batch no. LFD0350A.

Treatment R: Reference – 1 tablet Microgynon ® (levonorgestrel 0.15 mg + ethinylestradiol 0.03 mg) Batch no. 42376H.

A 28 day wash-out period was observed between administration of test and references. Serial blood samples (1 pre-dose sample and 19 samples within 72 h post dose) were taken during each study period to obtain bioavailability characteristics AUC, Cmax and tmax for bioequivalence evaluation. Drug concentrations for levonorgestrel and ethinyl estradiol were analyzed using a validated LC-MS/MS method. The limit of quantification was stated to be about 0.02 ng/ml for levonorgestrel and 5 pg/ml for ethinylestradiol.

The study was performed with 40 participants; data generated from a total of 37 subjects were utilized for analysis to establish pharmacokinetic parameters and assess bioequivalence.

Arithmetic mean and geometric mean values of the pharmacokinetic variables for levonorgestrel and ethinylestradiol as well as statistical results are summarised in the following tables:

**Levonorgestrel**

| **Pharmacokinetic Parameter** | **Test formulation (T)** arithmetic mean ± SD (geometric mean) | **Reference (R)** arithmetic mean ± SD (geometric mean) | **log-transformed parameters** | |
|---|---|---|---|---|
| | | | **Ratio** T/R (%) | **Conventional** 90% CI (ANOVAlog) |
| $t_{max}$ (h) | 1.2 ± 0.3 | 1.2 ± 0.6 | – | – |
| $C_{max}$ (ng/mL) | 4.22 ± 1.73 (3.90) | 4.50 ± 1.50 (4.26) | 91.5 | 85.9 – 97.5 |
| $AUC_{0-72h}$ (ng·h/mL) | 47.5 ± 19.4 (43.7) | 46.4 ± 18.0 (43.3) | 101.0 | 95.8 – 106.5 |

**Ethinylestradiol**

| **Pharmacokinetic Parameter** | **Test formulation (T)** arithmetic mean ± SD (geometric mean) | **Reference (R)** arithmetic mean ± SD (geometric mean) | **log-transformed parameters** | |
|---|---|---|---|---|
| | | | **Ratio** T/R (%) | **Conventional** 90% CI (ANOVAlog) |
| $t_{max}$ (h) | 1.5 ± 0.3 | 1.5 ± 0.4 | – | – |
| $C_{max}$ (pg/mL) | 67.9 ± 21.9 (64.8) | 65.6 ± 17.5 (63.5) | 102.0 | 95.7 – 108.7 |
| $AUC_{0-t}$ (pg·h/mL) | 753 ± 220 (722) | 719 ± 209 (692) | 104.4 | 99.6 – 109.4 |
| $AUC_{0-inf}$ (pg·h/mL) | 787 ± 236 -- | 755 ± 222 -- | – | – |

The results of the study show that preset acceptance limits of 80-125 % are met by both AUC and $C_{max}$ values regarding levonorgestrel and ethinylestradiol. Accordingly, the test Levonorgestrel/Ethinyl-Estradiol 0.15/0.03 mg FDC tablet meets the criteria for bioequivalence with regard to the rate and extent of absorption and is therefore bioequivalent to the reference formulation Microgynon ® (Bayer Schering Pharma AG).

## 4. Summary of product safety and efficacy

[RH071 trade name] has been shown to conform to the same relevant standards of quality, efficacy and safety as those required of the comparator product. According to the submitted data on quality and bioavailability, [RH071 trade name] is pharmaceutically and therapeutically equivalent and thus interchangeable with the comparator product Microgynon ® (Bayer Schering Pharma AG) for which benefits have been proven in terms of clinical efficacy. The clinical safety of [RH071 trade name] is considered acceptable when guidance and restrictions stated in the summary of product characteristics (SmPC) are considered. Refer to the SmPC (WHOPAR part 4) for data on clinical safety.

## 5. Benefit risk assessment and overall conclusion

### Quality

Physicochemical and biological aspects relevant to the uniform pharmaceutical characteristics have been investigated and are controlled in a satisfactory way. The quality of this product is considered to lead to an acceptable clinical performance when [RH071 trade name] is used in accordance with the SmPC.

### Bioequivalence

[RH071 trade name] has been shown to be bioequivalent with Microgynon ® (Bayer Schering Pharma AG).

### Efficacy and Safety

Regarding clinical efficacy and safety, [RH071 trade name] is considered effective and safe to use when the guidance and restrictions in the SmPC are taken into consideration.

**Benefit Risk Assessment**

Based on WHO's assessment of data on quality, bioequivalence, safety and efficacy the team of assessors considered that the benefit–risk profile of [RH071 trade name] was acceptable for the following indication: 'oral combined hormonal contraceptive (CHC) agent for women', and would allow inclusion of [RH071 trade name], manufactured at Laboratorios Leon Farma SA, C/La Vallina s/n, Poligono Industrial Navatejera, Villaquilambre, Leon 24008, Spain, in the list of prequalified medicinal products.