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	[RH067 trade name][*]
Manufacturer of Prequalified Product	Laboratorios Leon Farma SA
Active Pharmaceutical Ingredient(s) (API)	Ethinylestradiol / Desogestrel
Pharmaco-therapeutic group (ATC Code)	Progestogens and oestrogens, fixed combinations (G03AA09)
Therapeutic indication	[RH067 trade name] is an oral combined hormonal contraceptive (CHC) agent for women.

1. Introduction

[RH067 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 Ingredients (APIs)

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 desogestrel and ethinylestradiol. 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 are justified based on the stability results when the APIs are stored in the original packaging.

Other ingredients

Other ingredients used in the core of the active tablet formulation include lactose monohydrate, maize starch, povidone (E1201), d-alpha-tocopherol (E307), soybean oil, silica colloidal hydrated (E551), silica colloidal anhydrous (E551) and stearic acid (E570), all being pharmacopoeial controlled. The commercially sourced proprietary film-coating mixture contains hypromellose (E464), triacetin (E1518), polysorbate and titanium dioxide (E171) which are controlled by acceptable specifications. BSE/TSE compliance declarations were provided for all the excipients.

Finished pharmaceutical product (FPP)

Pharmaceutical development and manufacture

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

The multisource product consists of a white, round, biconvex film- coated tablet with **C** and **7** debossed on opposite sides (active tablet). The tablets are packaged in a PVC/PVDC-aluminium blister card. Each blister card contains 21 active tablets (white).

The aim of the formulation development was to develop a product bioequivalent to the comparator product, Microdiol® tablets (desogestrel/ethinylestradiol 0.15mg/0.03mg). The excipients used in the multisource product were selected based upon the comparator product. The excipients are all of pharmaceutical grade and are routinely used in pharmaceutical formulations. Direct compression manufacturing process was selected as the best option based on ease of manufacturing and product performance.

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 tablet include tests for appearance, identification of the APIs (HPLC and UV) and vitamin E (d-alpha-tocopherol) (UPLC), water content, assay of the APIs (HPLC), assay of vitamin E (UPLC), dissolution (HPLC detection), uniformity of dosage units (by content uniformity), related substances (HPLC) and microbial limits.

Stability testing

Stability studies have been conducted at 25°C/60%RH (zone II), 30°C/65%RH (zone IVa) and 30°C/75%RH (zone IVb) as long-term storage conditions and for six months at accelerated condition in the packaging intended for marketing of the product. The data provided show that there is some degradation of the APIs at the zone IVb storage condition, though the product proved to be quite stable at the zone II condition. 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 2011 according to internationally accepted guidelines:

Randomised, open-label, 2-way crossover, bioequivalence study of Laboratorios Leon Farma ethinyl estradiol-desogestrel 0.03mg-0.15mg tablets and Microdiol (reference) following a 1 x 0.03mg-0.15mg dose in healthy subjects under fasting conditions (study no. 110071).

The objective of the study was to compare the bioavailability of the stated Desogestrel/Ethinyl-estradiol 0.15mg/0.03mg FDC tablet manufactured by/for Laboratorios Leon Farma S.A., Spain (test drug) with the reference formulation Microdiol® (Schering-Plough) 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 Desogestrel/Ethinyl-estradiol 0.15mg/0.03mg (desogestrel 0.15 mg + ethinyl-estradiol 0.03mg) Batch no. LFD0065A.
Treatment R:	Reference – 1 tablet Microdiol® (desogestrel 0.15 mg + ethinyl-estradiol 0.03mg) Batch no. 689686.

A 28 day wash-out period was observed between administration of test and reference. Serial blood samples (1 pre-dose sample and 19 samples within 72h post dose) were taken during each study period to obtain bioavailability characteristics AUC, C_{max} and t_{max} for bioequivalence evaluation. Drug concentrations for 3-keto-desogestrel and ethinyl-estradiol were analyzed using a validated LC-MS/MS method. The limit of quantification was stated to be about 25 pg/mL for 3-keto-desogestrel and about 1 pg/mL for ethinyl-estradiol.

The study was performed with 60 participants; data generated from a total of 58 subjects were utilized for analysis to establish pharmacokinetic parameters and assess bioequivalence.

Arithmetic mean and geometric mean values of the pharmacokinetic variables for 3-keto-desogestrel and ethinyl-estradiol as well as statistical results are summarised in the following tables:

3-keto-desogestrel

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)	1.37 ± 0.40	1.78 ± 0.78	-	-
C_{max} (pg/mL)	1340 ± 391 (1286)	1409 ± 490 (1329)	96.9	90.6 – 103.5
$AUC_{0\text{-}72h}$ (pg·h/mL)	9764 ± 3848 (9222)	10229 ± 4526 (9575)	96.6	93.9 – 99.4

Ethinyl-estradiol

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)	1.48 ± 0.31	1.40 ± 0.27	-	-
C_{max} (pg/ml)	69 ± 21 (66)	74 ± 22 (71)	92.7	89.3 – 96.1
$AUC_{0\text{-}t}$ (pg.h/ml)	710 ± 249 (676)	711 ± 215 (681)	99.3	95.4 – 103.3
$AUC_{0\text{-}inf}$ (pg.h/ml)	772 ± 356 (725)	754 ± 220 (725)	100.1	95.3 – 105.3

The results of the study show that preset acceptance limits of 80 -125 % are met by both AUC and C_{max} values regarding 3-keto-desogestrel and ethinyl-estradiol. Accordingly, the test Desogestrel/Ethinyl-estradiol 0.15mg/0.03mg FDC tablet meets the criteria for bioequivalence with regard to the rate and extent of absorption and is therefore bioequivalent to the reference formulation Microdiol® (Schering-Plough).

4. Summary of product safety and efficacy

[RH067 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, [RH067 trade name] is pharmaceutically and therapeutically equivalent and thus interchangeable with the comparator product Microdiol® (Schering-Plough) for which benefits have been proven in terms of clinical efficacy. The clinical safety of [RH067 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.

2. 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 [RH067 trade name] is used in accordance with the SmPC.

Bioequivalence

[RH067 trade name] has been shown to be bioequivalent with Microdiol® (Schering-Plough).

Efficacy and Safety

Regarding clinical efficacy and safety, [RH067 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 [RH067 trade name] was acceptable for the following indication: 'oral combined hormonal contraceptive (CHC) agent for women', and would allow inclusion of [RH067 trade name], manufactured at Laboratorios Leon Farma SA, C/La Vallina s/n, Poligono Industrial Navatejera, Villaquilambre, Leon 24193, Spain, in the list of prequalified medicinal products.