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	[RH096 trade name]*
Manufacturer of Prequalified Product	HLL Lifecare Limited (A Government of India Enterprise) Unipill Block Kanagala Belagavi District Karnataka 591225 India
Active Pharmaceutical Ingredient(s) (API)	Ethinylestradiol / Levonorgestrel
Pharmaco-therapeutic group (ATC Code)	Progestogens and oestrogens, fixed combinations (G03AA07)
Therapeutic indication	Oral combined hormonal contraceptive (CHC) agent for women

1. Introduction

[RH096 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)

Ethinylestradiol and levonorgestrel have been prequalified by WHO according to WHO's Procedure for assessing the acceptability, in principle, of active pharmaceutical ingredients for use in in pharmaceutical products (WHO Technical Report Series No. 953, 2009, Annex 4). This procedure provides an assurance that the APIs, used in the manufacture of [RH096 trade name] are of good quality and manufactured in accordance with WHO Good Manufacturing Practices (GMP). API prequalification consists of a comprehensive evaluation procedure that has two components: Assessment of the API master file (APIMF) to verify compliance with WHO norms and standards, and inspection of the sites of API manufacture to verify compliance with WHO GMP requirements.

Ethinylestradiol and levonorgestrel are of BCS low solubility, hence particle size distribution (PSD) is considered a critical parameter and forms part of the FPP manufacturer's API specifications. The acceptance criteria for PSD were set on information of the API lots used in the FPP biobatch.

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

Other ingredients

Other ingredients used in the core tablet formulation include lactose monohydrate, maize starch, poloxamer, povidone, colloidal silicon dioxide and magnesium stearate, all being pharmacopoeial controlled. The commercially sourced proprietary film-coating mixture contains polyvinyl alcohol, partially hydrolyzed, titanium dioxide, macrogol/PEG, talc, iron oxide yellow and iron oxide red. BSE/TSE compliance declarations were provided for all the excipients.

Finished pharmaceutical product (FPP)

Pharmaceutical development and manufacture

The multisource product is a round, biconvex, yellow, film-coated tablet of about 6 mm in diameter, debossed with "C1" on one side and plain on the other side. The tablets are packaged in clear PVC/PVDC-Alu blister cards.

[RH096 trade name] has been developed as a generic version of the WHO recommended comparator product, Levora® 0.15/30-28. The selection of the excipients was based on the excipients used in the comparator product and information from the Inactive Ingredient Database (IID) of the USFDA. The wetting agent Poloxamer 407 was included to enhance the dissolution rate of the poorly soluble APIs. Results of compatibility studies confirmed the compatibility of all the selected excipients with the APIs.

Content uniformity is regarded a critical quality attribute of the low API load tablet. Direct compression may lead to blend segregation during compression and thereby compromise content uniformity. Hence, direct compression was not considered an acceptable process for this formulation. A wet granulation process, with the API introduced in the dissolved form in an organic solvent, was excluded because of the desire to avoid the environmental considerations involved. An aqueous based wet granulation process, with the APIs dry mixed with excipient blend, was selected for the manufacture of the tablets. The selected process facilitated formation of uniform free flowing granules along with interlocking of the APIs within these formed granules. The resulted interlocking of APIs in the granules minimized the blend segregation during compression as reflected by content uniformity results of manufactured tablets. Various experiments were performed to select and optimize the concentration of excipients and other process parameters to obtain coated tablets of desired characteristics. Satisfactory in-process controls have been established.

According to a risk evaluation by the applicant, the FPP has no potential to contain nitrosamine impurities and hence no risk was identified.

Specifications

The finished product specifications include tests for description, identification of APIs (HPLC and TLC), average weight, thickness, tablet dimensions, hardness, friability, disintegration time, loss on drying, uniformity of content (HPLC), assay (HPLC), dissolution (HPLC detection), related substances (HPLC) and microbiological purity. The test procedures have been adequately validated.

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 indicates that the product is stable at these storage conditions, with no apparent negative trend with respect to chemical attributes. 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 2020 according to internationally accepted guidelines.

A randomized, single blind, balanced, two-treatment, two-period, two-sequence, single dose, crossover bioequivalence study of Ethinylestradiol/Levonorgestrel 30 µg/150 µg film coated tablets of HLL Lifecare Ltd., India ([RH096 trade name]), with LEVORA® 0.15/30-28 (levonorgestrel and ethinyl estradiol tablets USP, 0.15 mg/0.03 mg) of Mayne Pharma, LLC, US, in normal, healthy, adult, non-pregnant female human subjects under fasting conditions (study no. ARL/18/236).

The objective of the study was to compare the bioavailability of the stated Ethinylestradiol/ Levonorgestrel 0.03/0.15 mg FDC tablet manufactured by/for HLL Lifecare Ltd., India (test drug) with the reference formulation Levora® (Mayne Pharma, LLC) and to assess bioequivalence. The comparison was performed as a single centre, single blind, 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 [RH096 trade name]
(ethinyl estradiol 0.0 mg + levonorgestrel 0.15 mg)
Batch no. C1B003G.

Treatment R: Reference – 1 tablet Levora®
(ethinyl estradiol 0.03 mg + levonorgestrel 0.15 mg)
Batch no. CCFPS.

A 21 day wash-out period was observed between administration of test and references. Serial blood samples (1 pre-dose sample and 18 samples within 72 h post dose) were taken during each study period to obtain bioavailability characteristics AUC, C_{max} and t_{max} for bioequivalence evaluation. Drug concentrations for ethinyl estradiol and levonorgestrel were analyzed using validated LC-MS/MS methods. The limit of quantification was stated to be about 1 pg/mL for ethinyl estradiol and 50 pg/mL for levonorgestrel.

The study was performed with 36 participants; data generated from a total of 34 subjects were used for analysis to establish pharmacokinetic parameters and assess bioequivalence.

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

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)	1.74 ± 0.48	1.61 ± 0.42	–	–
C_{max} (pg/mL)	84.6 ± 23.8 (81.2)	85.4 ± 25.7 (81.7)	99.4	94.8 – 104.3
AUC_{0-t} (pg·h/mL)	975 ± 314 (924)	987 ± 321 (938)	98.6	95.3 – 102.0

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)	1.19 ± 0.53	1.16 ± 0.68	–	–
C_{max} (ng/mL)	4.01 ± 1.71 (3.69)	3.91 ± 2.34 (3.50)	105.6	94.4 – 118.1
$AUC_{0\text{-}72h}$ (ng·h/mL)	47.1 ± 23.9 (42.3)	50.2 ± 45.4 (41.9)	100.8	91.3 – 111.3

4. Summary of product safety and efficacy

[RH096 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, [RH096 trade name] is pharmaceutically and therapeutically equivalent and thus interchangeable with the comparator product Levora® (Mayne Pharma, LLC) for which benefits have been proven in terms of clinical efficacy. The clinical safety of [RH096 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 [RH096 trade name] is used in accordance with the SmPC.

Bioequivalence

[RH096 trade name] has been shown to be bioequivalent with Levora® (Mayne Pharma, LLC).

Efficacy and Safety

Regarding clinical efficacy and safety, [RH096 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 [RH096 trade name] was acceptable for the following indication: 'an oral combined hormonal contraceptive (CHC) agent for women', and would allow inclusion of [RH096 trade name], manufactured at HLL Lifecare Limited, Kanagala, Karnataka, 591225 India in the list of prequalified medicinal products.