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	[RH065 trade name][*]
Manufacturer of Prequalified Product	HLL Lifecare Limited (A Govt. of India Enterprise) Unipill Block Kanagala Belagavi (District) Karnataka India–591225
Active Pharmaceutical Ingredient (API)	Levonorgestrel
Pharmaco-therapeutic group (ATC Code)	Sex hormones and modulators of the genital system, emergency contraceptives (G03AD01)
Therapeutic indication	[RH065 trade name] is indicated for emergency contraception in women.

1. Introduction

[RH065 trade name] is indicated for emergency contraception within 72 hours of unprotected sexual intercourse or failure of a contraceptive method in women.

[RH065 trade name] should be initiated by a health care provider experienced in the management of emergency contraception.

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)

Levonorgestrel used in the manufacture of [RH065 trade name] has been prequalified by WHO according to WHO's Procedure for assessing the acceptability, in principle, of active pharmaceutical ingredients for use in pharmaceutical products (WHO Technical Report Series No. 953, 2009, Annex 4). This procedure provides an assurance that levonorgestrel, used in the manufacture of Unipill, is of good quality and manufactured in accordance with WHO Good Manufacturing Practices. 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 assessment of the sites of API manufacture to verify compliance with WHO GMP requirements.

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

Levonorgestrel is critically insoluble (of BCS low solubility across the physiological pH range), 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 lot used in the manufacture of the FPP biobatch.

Other ingredients

Other ingredients include lactose monohydrate, maize starch, poloxamer, povidone, colloidal silicon dioxide and magnesium stearate. The magnesium stearate used in the manufacture of this product is of vegetable origin. The lactose monohydrate is of bovine origin and animal enzymes are not used in its production. The supplier of lactose monohydrate attested that the material is free from TSE/BSE contamination.

Finished pharmaceutical product (FPP)

Pharmaceutical development and manufacture

The multisource product is an almost white, flat, round, uncoated tablet, about 8 mm in diameter, debossed with "UP" on one side and plain on the other side. The tablets are packaged in clear PVC/PVDC-Alu blister cards, with one tablet packed per blister card.

[RH065 trade name] has been developed as a generic version of the WHO recommended comparator product, Plan B One-Step®. 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 critically insoluble API. Results of compatibility studies confirmed the compatibility of all the selected excipients with the API.

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 API introduced in the dispersed form in water, was selected for the manufacture of the tablets. The selected process facilitated formation of uniform free flowing granules along with interlocking of the API within these formed granules. The resulted interlocking of API in the granules minimized the blend segregation during compression as reflected by content uniformity results of manufactured tablets.

Specifications

The product specifications include tests for description, identification (HPLC, IR), uniformity of mass, thickness, hardness, disintegration time, friability, loss on drying, dissolution (HPLC detection), uniformity of content, assay (HPLC), related substances (HPLC) and microbiological purity. The analytical 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 40°C/75%RH as accelerated condition in the packaging proposed for marketing of the product. The FPP proved to be quite stable at both 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 2015 according to internationally accepted guidelines.

Study title:

A randomized, single blind, balanced, two-treatment, two-period, two-sequence, single dose, crossover, bioequivalence study of Levonorgestrel tablets 1.5 mg of HLL Lifecare Limited, India with Plan B One-Step (levonorgestrel) tablets 1.5 mg of Gedeon Richter, Ltd., Budapest, Hungary for Teva Women's Health, Inc. in normal, healthy, adult, female human subjects under fasting condition (study no. ARL/15/358).

The objective of the study was to compare the bioavailability of the stated Levonorgestrel tablets 1.5 mg manufactured by/for HLL Lifecare Limited, India (test drug) with the reference formulation Plan B One-Step® tablets 1.5 mg (Gedeon Richter Ltd.) 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 [RH065 trade name]
	(levonorgestrel 1.5 mg)
	Batch no. LN03UV/15003.
Treatment R:	Reference – 1 tablet Plan B One-Step®
	(levonorgestrel 1.5 mg)
	Batch no. 33807084A.

A 28 day wash-out period was observed between administration of test and reference. Serial blood samples (1 pre-dose sample and 22 samples within 72 hours post-dose) were taken during each study period to obtain bioavailability characteristics AUC, Cmax and tmax for bioequivalence evaluation. Drug concentrations for levonorgestrel were analyzed using a validated LC-MS/MS method. The limit of quantification was stated to be about 0.15 ng/ml for levonorgestrel.

The study was performed with 30 participants. Data generated from a total of 27 subjects were utilized for analysis to establish pharmacokinetic parameters and assess bioequivalence.

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

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)	1.91 ± 0.90	3.03 ± 1.12	-	-
C_{max} (ng/mL)	17.2 ± 5.7 (16.4)	16.3 ± 4.1 (15.8)	103.8	96.8 – 111.3
AUC_{0-72h} ({unit}·h/mL)	274 ± 98 (259)	292 ± 103 (274)	94.5	89.1 – 100.3

The results of the study show that preset acceptance limits of 80 -125 % are met by both AUC and C_{max} values regarding levonorgestrel. Accordingly, the test [RH065 trade name] meets the criteria for bioequivalence with regard to the rate and extent of absorption and is therefore, bioequivalent to the comparator product Plan B One-Step® (Gedeon Richter Ltd.).

4. Summary of product safety and efficacy

[RH065 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, [RH065 trade name] is pharmaceutically and therapeutically equivalent and thus interchangeable with the comparator product Plan B One-Step® (Gedeon Richter Ltd.) for which benefits have been proven in terms of clinical efficacy. The clinical safety of [RH065 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 [RH065 trade name] is used in accordance with the SmPC.

Bioequivalence

[RH065 trade name] has been shown to be bioequivalent with Plan B® One-Step (Gedeon Richter Ltd).

Efficacy and Safety

Regarding clinical efficacy and safety, [RH065 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 [RH065 trade name] was acceptable for the following indication: ' **emergency contraception within 72 hours of unprotected sexual intercourse or failure of a contraceptive method in women** ', and would allow inclusion of [RH065 trade name], manufactured at HLL Lifecare Limited, (A Govt. of India Enterprise), Unipill Block, Kanagala, Belagavi (District), Karnataka, 591225, India in the list of prequalified medicinal products.