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	[RH046 trade name][1]
Manufacturer of Prequalified Product:	Cipla Limited Unit VIII, Goa M/s Cipla Ltd, L-147 to L-147-1 Verna Industrial estate, Verna Goa India
Active Pharmaceutical Ingredient (API)	Levonorgestrel
Pharmaco-therapeutic group **(ATC Code)**	Progestogen (G03AD01)
Therapeutic indication:	[RH046 trade name] is indicated for emergency contraception within 72 hours of unprotected sexual intercourse or failure of a contraceptive method

1. Introduction

[RH046 trade name] is indicated for emergency contraception within 72 hours of unprotected sexual intercourse or failure of a contraceptive method.

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 Levonorgestrel 1.5mg Tablets 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 Levonorgestrel 1.5mg Tablets, 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.

Other ingredients

Other ingredients include lactose monohydrate, maize starch, povidone, colloidal anhydrous silica and magnesium stearate. Magnesium stearate is of vegetable origin. The supplier of lactose monohydrate attested that the material is free from TSE/BSE contamination.

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

Finished pharmaceutical product (FPP)

Pharmaceutical development and manufacture

The product is a white to off-white, circular, flat, bevelled, uncoated tablet plain on both sides. The tablets are packaged in clear PVC/PE/PVDC-aluminium blisters (one tablets per card).

The development of the final composition of product has been described. The aim was to develop a stable product, which would be of similar quality and bioequivalent to the comparator product, Plan B® One-Step (containing 1.5 mg levonorgestrel). The comparator product was characterized in support of the development and for defining a quality target product profile. The excipients selected are similar to those of the comparator product, with povidone additionally included. An aqueous wet granulation process, designed to achieve uniform distribution of levonorgestrel, was selected for manufacture of the tablets. Optimization studies included targeting of dissolution profiles of the comparator product. Appropriate in-process controls were set to ensure batch-to-batch reproducibility.

Specifications

The product specifications include tests for description, identification (HPLC, UV), average weight, uniformity of weight, water content, friability, hardness, disintegration time, dissolution (HPLC detection), uniformity of dosage units (by content uniformity), assay (HPLC), degradation products (HPLC), and microbiological examination of non-sterile products. The analytical procedures have been adequately validated.

Stability testing

Stability studies have been conducted at 30°C/75%RH as long-term storage conditions and for six months at accelerated conditions 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. 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 2010 according to internationally accepted guidelines.

Study Title: An open-label randomized, single oral dose, two way crossover bioequivalence study to compare Levonorgestrel tablet 1.5 mg (Perrigo® Company USA) with Plan B® One-Step (containing levonorgestrel tablet 1.5mg) (Mfg. by Gedeon Richter, Ltd., Budapest, Hungary for Duramed Pharmaceuticals, Inc., Subsidiary of Barr Pharmaceuticals, Inc. Pomona, New York 10970., USA) in 72 healthy, adult, human female study participants under fasting conditions. (study no. 14208/09-10).

The objective of the study was to compare the bioavailability of the stated Levonorgestrel 1.5 mg tablet manufactured for/by Perrigo® Company, USA (test drug) with the reference formulation Plan B® (Duramed Pharmaceuticals Inc.) and to assess bioequivalence. The comparison was performed as a single oral dose, open label, randomized, crossover study in healthy subjects under fasting conditions. Each subject was assigned to receive each of the following treatments in a randomized fashion:

Treatment T:	Test – 1 tablet levonorgestrel 1.5 mg (levonorgestrel 1.5 mg) Batch no. X05194.
Treatment R:	Reference – 1 tablet Plan B® (levonorgestrel 1.5 mg) Batch no. T91196A4

A 14 day wash-out period was observed between administration of test and reference. Serial blood samples (1 pre-dose sample and 26 samples within 120 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 levonorgestrel were analysed using a validated LC-MS/MS method. The limit of quantification was stated to be about 0.5 ng/ml for levonorgestrel.

The study was performed with 72 participants; data generated from a total of 67 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:

Pharmacokinetic Parameter	Test formulation (T) arithmetic mean ± SD (*)	Reference (R) arithmetic mean ± SD (*)	log-transformed parameters	
			Ratio T/R (%)	Conventional 90% CI (ANOVAlog)
t_{max} (h)	2.33 (0.75 – 6.0)#	2.67 (1.0 – 5.0)	-	-
C_{max} (ng/ml)	19.3 ± 6.9 (18.3)	20.3 ± 8.2 (18.9)	96.9	90.6 – 103.6
AUC_{0-t} (ng.h/ml)	397 ± 197 (350)	385 ± 204 (337)	103.7	93.8 – 114.6
AUC_{0-inf} (ng.h/ml)	443 ± 214 (394)	424 ± 214 (376)	104.8	94.3 – 116.5

* geometric mean; # median (minimum-maximum)

The results of the study show that present acceptance limits of 80 -125 % are met by both AUC and C_{max} values regarding levonorgestrel. Accordingly, the test tablet Levonorgestrel 1.5 mg meets the criteria for bioequivalence with regard to the rate and extent of absorption and is therefore bioequivalent to the reference Plan B® (Duramed Pharmaceuticals Inc.).

4. Summary of product safety and efficacy

[RH046 trade name] conforms to the same appropriate standards of quality, efficacy and safety as those required of the innovator's product. According to the submitted data on quality and bioavailability it is pharmaceutically and therapeutically equivalent to the reference Plan B®.

The clinical safety of this product is considered acceptable when guidance and restrictions presented in the Summary of Product Characteristics are taken into consideration. Reference is made to the SmPC (WHOPAR Part 4) for data on clinical safety.

5. Benefit risk assessment and overall conclusion

Quality

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

Bioequivalence

[RH046 trade name] was determined to be qualitatively essentially the same with the Plan B® (Duramed Pharmaceuticals Inc.), the ratio of active ingredients and excipients between the strengths is considered essentially the same, and the dissolution profiles between the formulations for the APIs were determined to be similar.

Efficacy and Safety

Regarding clinical efficacy and safety, [RH046 trade name] is considered effective and safe when the guidance and restrictions presented in the SmPC are taken into consideration.

Benefit Risk Assessment

Based on the WHO assessment of data on quality, bioequivalence, safety and efficacy the team of assessors considered by consensus that the benefit–risk profile of [RH046 trade name] was acceptable

for the following indications: **"emergency contraception within 72 hours of unprotected sexual intercourse or failure of a contraceptive method"**, and has advised inclusion of [RH046 trade name], manufactured at Cipla Limited, Unit VIII, Goa, M/s Cipla Ltd, L-147 to L-147-1, Verna Industrial estate, Verna Goa, India in the list of prequalified medicinal products.