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	[RH040 trade name][*]
Manufacturer of Prequalified Product	Cipla Limited[†] Unit VIII, Goa m/s Cipla Ltd, L-147 to L-147-1 Verna Industrial Estate Verna Goa 403 722 India
Active Pharmaceutical Ingredient(s) (API)	Levonorgestrel
Pharmaco-therapeutic group (ATC Code)	Progestogen (G03AD01)
Therapeutic indication	[RH040 trade name] is indicated for emergency contraception.

†Manufacturing site at time of prequalification. For updated address of manufacturing site see patient information leaflet (part3 of this WHOPAR).

1. Introduction

[RH040 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 is an established API described in the Ph.Int., Ph.Eur. and USP. It is practically insoluble in water, with solubility about 1 µg/ml at 37ºC over the physiological pH range according to data provided. The molecule contains 6 stereogenic carbon centres. The API is manufactured as the pure stereoisomer in multiple steps.

The API specifications are pharmacopoeial based and include tests for description, solubility, identification, specific optical rotation, related substances (HPLC), loss on drying, sulphated ash, assay, heavy metals, enantiomeric purity (HPLC), residual solvents and nickel.

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

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

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.

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 (2 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®. 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. A wet granulation process, with levonorgestrel introduced in the dissolved form in an organic solvent to improve content uniformity, was selected. Optimisation 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 are pharmacopoeial based and include tests for description, identification, average mass, uniformity of mass, hardness, friability, disintegration time, water content, dissolution, uniformity of dosage units (by content uniformity), assay (HPLC), degradation products (HPLC), residual solvent 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. The FPP proved to be quite stable at both storage conditions, showing a slight increase in degradation products with time. 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 2008 according to internationally accepted guidelines:

Single-dose, two-way crossover , bioequivalence study of Levonorgestrel 0.75 mg tablets in healthy female subjects under fasted conditions (study no. S08-0141).

The objective of the study was to compare the bioavailability of the stated Levonorgestrel 0.75 mg tablet ([RH040 trade name]), manufactured by Cipla Ltd, India (test drug) with the same dose of the reference formulation (Plan B®, Gedeon Richter Ltd.) and to assess bioequivalence. The comparison was performed as a single-centre, open-label, randomised, crossover study in healthy female subjects under fasting conditions. Each subject was assigned to receive each of the following two treatments in a randomised fashion:

Treatment T:	Test – 1 tablet [RH040 trade name] (levonorgestrel 0.75 mg) Batch no. X85110.
Treatment R:	Reference – 1 tablet Plan B®

(levonorgestrel 0.75 mg)
Batch no. T72207A.

A 14-day wash-out period was observed between the administration of test and reference. Serial blood samples (1 pre-dose sample and 22 samples within 120 hours after the 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 250 pg/ml.

The study was performed with 34 participants; data generated from a total of 33 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 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)	1.46 ± 0.67	1.76 ± 0.96	–	–
C_{max} (pg/mL)	13165 ± 5687 (12027)	11532 ± 5301 (10548)	114.0	104.1–124.9
AUC_{0-t} (pg·h/mL)	149171 ± 104160 (127683)	139315 ± 86270 (121653)	105.0	96.1–114.6
AUC_{0-inf} (pg·h/mL)	160216 ± 107326 (139400)	151678 ± 86958 (135249)	103.1	95.1–111.8

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 tablet [RH040 trade name] meets the criteria for bioequivalence with regard to the rate and extent of absorption and is therefore bioequivalent to the reference Plan B® (Gedeon Richter Ltd.).

4. Summary of product safety and efficacy

[RH040 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, [RH040 trade name] is pharmaceutically and therapeutically equivalent and thus interchangeable with the comparator product, Plan B®, for which benefits have been proven in terms of clinical efficacy.

The clinical safety of [RH040 trade name] is considered acceptable when guidance and restrictions stated in the Summary of Product Characteristics (SmPC) are taken into consideration. Refer 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 SPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

Bioequivalence

[RH040 trade name] was determined to be qualitatively essentially the same as Plan B® (Gedeon Richter Ltd.), 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, [RH040 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 [RH040 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 [RH040 trade name], manufactured at Cipla Limited, Verna Goa, India, in the list of prequalified medicinal products.