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:	[RH032 trade name] *
Manufacturer of Prequalified Product:	Famy Care Limited Plot No. 20 & 21, Pharmez Pharmaceutical Special Economic Zone (SEZ) Sarkhej, near Matoda Village Ahmedabad India
Active Pharmaceutical Ingredients (APIs):	Levonorgestrel
Pharmaco-therapeutic group (ATC Code):	Progestogen (G03AD01)
Therapeutic indication:	[RH032 trade name] is indicated for emergency contraception.

1. Introduction

[RH032 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 according to SOP 20 of the WHO Prequalification Programme.

Active pharmaceutical Ingredients (APIs)

All aspects of the manufacture and control of levonorgestrel are supported by the EDQM Certificate of Suitability (CEP). The API is in the micronized form and product appropriate specifications have been set for particle size distribution.

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 packing material.

Other ingredients

Other ingredients include povidone, lactose monohydrate, maize starch, colloidal silicon dioxide and magnesium stearate. Magnesium stearate is of vegetable origin.

* Trade names are not prequalified by WHO. This is the national medicines regulatory authority's (NMRA) responsibility. Throughout this WHOPAR the proprietary name is given as an example only.

Finished pharmaceutical product (FPP)

[RH032 trade name] is a round, white to off-white, uncoated flat tablet, debossed '207' on one side and plain on the other side. The tablets are packaged in PVC/PVdC-aluminium blister cards (2 tablets per card).

Pharmaceutical development and manufacture
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, was selected. Optimization studies included targeting of the disintegration time and dissolution profiles of the comparator product. Appropriate in-process controls, including blend uniformity, were set to ensure batch-to-batch reproducibility.

Specifications
The finished product specifications are regarded adequate for ensuring consistent quality and include tests for description, identification (HPLC and TLC), water content (KF), dissolution, uniformity of dosage units (by content uniformity), assay (HPLC), related substances (HPLC), residual solvents and microbial enumeration. 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 product 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 Bio-Equivalence

The following bioequivalence study has been performed in 2011 according to internationally accepted guidelines.

Single-dose fasting bioequivalence study of levonorgestrel tablets 750 µg and Plan B® tablets (0.75 mg: Duramed) in healthy female volunteers (study No. PLNB-09280).

The objective of the study was to compare the bioavailability of the stated levonorgestrel tablets 750 µg manufactured by Famy Care Ltd, India (test drug) with the same dose of the reference formulation (Plan B, Duramed) and to assess bioequivalence. The comparison was performed as a single-centre, 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 – levonorgestrel 750 µg tablets (levonorgestrel 0.75 mg) Batch no. 0612F001C.
Treatment R:	Reference – Plan B® tablet (levonorgestrel 0.75 mg) Batch no. T96566N.

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 120 hours after 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 0.10 ng/mL for levonorgestrel.

The study was performed with 34 participants. Data generated from a total of 30 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 (*)	Reference (R) arithmetic mean ± SD (*)	log-transformed parameters	
			Ratio T/R (%)	Conventional 90% CI (ANOVAlog)
t_{max} (hour)	2.47 ± 1.68	2.42 ± 1.24	–	–
C_{max} (ng/mL)	14.20 ± 4.83 (13.46)	13.97 ± 4.25 (13.48)	99.9	91.2–109.3
AUC_{0-t} (ng·hour/mL)	239 ± 102 (222)	243 ± 108 (226)	98.1	91.1–105.7
AUC_{0-inf} (ng·hour/mL)	252 ± 107 (235)	257 ± 112 (240)	97.9	90.8–105.5

* geometric mean

The results of the study show that the preset acceptance limits of 80–125 % are met by both AUC and C_{max} values regarding levonorgestrel. Accordingly, the test levonorgestrel 750 µg tablet meets the criteria for bioequivalence with regard to rate and extent of absorption and is therefore, bioequivalent to the reference Plan B® (Duramed).

4. Summary of Product Safety and Efficacy

[RH032 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 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

[RH032 trade name] was determined to be qualitatively essentially the same with the Plan B® (Duramed), 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, [RH032 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 [RH032 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 [RH032 trade name], manufactured at Famy Care Ltd Famy Care Limited, Plot No. 20 & 21, Pharmez Pharmaceutical Special Economic Zone (SEZ), Sarkhej, near Matoda Village, Ahmedabad, India, in the list of prequalified medicinal products.