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	[RH031 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 Ingredient(s) (API)	Levonorgestrel
Pharmaco-therapeutic group (ATC Code)	Progestogen (G03AD01)
Therapeutic indication	[RH031 trade name] is indicated for emergency contraception

1. Introduction

[RH031 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)

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.

Finished pharmaceutical product (FPP)

[RH031 trade name] is a round, white to off-white, uncoated flat tablet, debossed '145' on one side and plain on the other side. The tablet is packaged in PVC/PVdC-aluminium blister card (1 tablet per card).

* Trade names are not prequalified by WHO. This is the national medicines regulatory authority's responsibility.
† Formerly Famy Care Ltd then Jai Pharma Ltd then Mylan Laboratories Ltd.

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, Norlevo® 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 qualitatively similar to those of the comparator product. A wet granulation process, with levonorgestrel introduced in the dissolved form in an organic solvent, was selected. Optimization studies included targeting of the 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 30ºC/75%RH as long-term storage conditions and for six months at accelerated conditions in the packaging proposed for marketing of the product. 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 bioequivalence

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

An open-label, balanced, randomized, two-treatment, two-period, two-sequence, single oral dose, crossover, bioequivalence study of [RH031 trade name] of Famy Care Ltd, India, with that of Norlevo® (levonorgestrel) tablet 1.5 mg of HRA Pharma in healthy, adult, human female subjects under fasting conditions (study no. 207-11).

The objective of the study was to compare the bioavailability of the stated [RH031 trade name] manufactured by Famy Care Ltd., India (test drug) with the same dose of the reference formulation (Norlevo®, HRA Pharma) and to assess bioequivalence. The comparison was performed as a single-centre, open-label, randomized, crossover study in healthy female 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 [RH031 trade name] (levonorgestrel 1.5 mg) Batch no. 1607F003C.
Treatment R:	Reference – 1 tablet Norlevo® (levonorgestrel 1.5 mg) Batch no. LX023G.

A 28-day wash-out period was observed between administration of test and reference. Serial blood samples (1 pre-dose sample and 20 samples within 72 hours 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 analyzed using a validated LC-MS/MS method. The limit of quantification was stated to be about 0.2 ng/mL for levonorgestrel.

The study was performed with 36 participants. Data generated from a total of 34 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) #	2.13 (1–4)	2.13 (1–4)	–	–
C_{max} (ng/mL)	20.1 ± 6.6 (19.3)	17.5 ± 7.1 (16.3)	118.0	111.6–124.9
$AUC_{0\text{-}72h}$ (ng·h/mL)	318 ± 138 (289)	312 ± 153 (275)	105.2	98.5–112.3

median (range)

The results of the study show that the preset acceptance limits of 80–125% are met by both AUC and Cmax values regarding levonorgestrel. Accordingly, the test [RH031 trade name] meets the criteria for bioequivalence with regard to the rate and extent of absorption and is therefore, bioequivalent to the reference Norlevo® (HRA Pharma).

4. Summary of product safety and efficacy

[RH031 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, [RH031 trade name] is pharmaceutically and therapeutically equivalent and thus interchangeable with the comparator product Norlevo® (HRA Pharma) for which benefits have been proven in terms of clinical efficacy. The clinical safety of [RH031 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 [RH031 trade name] is used in accordance with the SmPC.

Bioequivalence

[RH031 trade name] has been shown to be bioequivalent with Norlevo® (HRA Pharma).

Efficacy and Safety

Regarding clinical efficacy and safety, [RH031 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 [RH031 trade name] was acceptable for the following indication: 'emergency contraception within 72 hours of unprotected sexual intercourse or failure of a contraceptive method', and would allow inclusion of [RH031 trade name], manufactured at 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.