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

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|---|---|
| **Name of the Finished Pharmaceutical Product** | [RH032 trade name]* |
| **Manufacturer of Prequalified Product** | Famy Care Limited<br>Plot No. 20 & 21, Pharmez<br>Pharmaceutical Special Economic Zone (SEZ)<br>Sarkhej, near Matoda Village<br>Ahmedabad<br>India |
| **Active Pharmaceutical Ingredient(s) (API)** | Levonorgestrel |
| **Pharmaco-therapeutic group (ATC Code)** | Progestogen (G03AD01) |
| **Therapeutic indication** | [RH032 trade name] is indicated for emergency contraception to prevent pregnancy following unprotected intercourse or a known or suspected contraceptive failure. |

## 1. Introduction

[RH032 trade name] is indicated for emergency contraception to prevent pregnancy following unprotected intercourse or a known or suspected contraceptive failure.

## 2. Assessment of quality

The assessment was done according to SOP 20 of the WHO Prequalification Programme.

### 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)

[RH032 trade name] are white to off-white, round uncoated tablets. They are flat on the top and bottom with a bevelled edge. The tablets have '207' debossed (stamped into) on one side and are plain

* 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 Limited.

on the other side. The tablets are packed in clear colourless plastic (PVC-PVdC) on Aluminium blister cards, containing two tablets. Available in cartons of 1 x 2 tablets.

*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 30ºC/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 bioequivalence

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

Single-dose fasting bioequivalence study of [RH032 trade name] 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 [RH032 trade name] manufactured by Famy Care Limited, 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:

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|---|---|
| Treatment T: | Test – [RH032 trade name] (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, Cmax and tmax 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 (geometric mean) | **Reference (R)** arithmetic mean ± SD (geometric mean) | **log-transformed parameters** | |
|---|---|---|---|---|
| | | | **Ratio** T/R (%) | **Conventional** 90% CI (ANOVAlog) |
| $t_{max}$ (h) | 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·h/mL) | 239 ± 102 (222) | 243 ± 108 (226) | 98.1 | 91.1–105.7 |
| $AUC_{0-inf}$ (ng·h/mL) | 252 ± 107 (235) | 257 ± 112 (240) | 97.9 | 90.8–105.5 |

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 [RH032 trade name] 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] 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, [RH032 trade name] is pharmaceutically and therapeutically equivalent and thus interchangeable with the comparator product Plan B® (Duramed) for which benefits have been proven in terms of clinical efficacy.

The clinical safety of [RH032 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 [RH032 trade name] is used in accordance with the SmPC.

### Bioequivalence

[RH032 trade name] has been shown to be bioequivalent with 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 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 [RH032 trade name] was acceptable for the following indication: ' emergency contraceptive to prevent pregnancy following unprotected intercourse or a known or suspected contraceptive failure', and would allow 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.