This part reflects the scientific knowledge and the information about this product available at the time of prequalification. Thereafter, updates may have become necessary which are included in parts 1 to 5 and, if related to pharmaceutical issues, also documented in part 8 of this WHOPAR.

SCIENTIFIC DISCUSSION

Name of the Finished Pharmaceutical Product:	**FAMY-POP 30 µg Tablets***
Manufacturer of Prequalified Product:	Jai Pharma Limited Plot No. 20/21, Pharmez The Pharmaceutical Special Economic Zone Sarkhej - Bavla National Highway No-8A, Nr. Village Matoda Taluka-Sanand Dist-Ahmedabad 382 213 Gujarat India
Active Pharmaceutical Ingredient (API):	Levonorgestrel
Pharmaco-therapeutic group (ATC Code):	Hormonal contraceptives for systemic use, progestogens (J03AC03)
Therapeutic indication:	Contraception for women

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

1. Introduction

FAMY-POP is indicated for oral contraception for women as detailed in the summary of product characteristics.

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 and polymorphic form.

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 used in the core tablet formulation include povidone, lactose monohydrate, colloidal silicon dioxide and magnesium stearate, all being pharmacopoeial controlled. The commercially sourced proprietary film-coating mixture contains hypromellose, titanium dioxide, polyethylene glycol/macrogol and talc. BSE/TSE compliance declarations were provided for all excipients.

Finished pharmaceutical product (FPP)

Pharmaceutical development and manufacture

The multisource product is a round, white to off-white, biconvex, film coated tablet, debossed with 'E' on one side and plain on other side. The tablets are packaged in PVC/PVdC-Al blisters containing 28 or 35 tablets per blister 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, Norgeston® containing 30µg levonorgestrel per tablet. The comparator product was characterized in support of the development and for defining a quality target product profile.

The excipients selected are commonly used in immediate release tablets and were shown to be compatible with levonorgestrel. A wet granulation process, with levonorgestrel introduced in the dissolved form in an organic solvent to ensure content uniformity in the low dose tablet, was selected. Optimization studies included targeting of 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 of the API (HPLC and TLC) and colorant, loss on drying, average weight, 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 of the product. The FPP proved to be quite stable at both storage conditions, with slight degradation observed though well within defined limits. 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 2014 according to internationally accepted guidelines.

Study title: An open label, balanced, randomized, two-treatment, two-period, two-sequence, single oral dose, crossover, bioequivalence study of Levonorgestrel tablets (3 x 30 µg) manufactured by Jai Pharma Limited, India, with that of Norgeston® (levonorgestrel 3 x 30 µg) tablets of Bayer Plc, Newbury, Berkshire in healthy, adult, human female subjects under fasting conditions (study no. 408-13).

The objective of the study was to compare the bioavailability of the stated Levonorgestrel 30 µg tablet manufactured by Jai Pharma Limited, India (test drug) with the reference formulation Nogeston® (Bayer Plc.) and to assess bioequivalence. The comparison was performed as a single centre, 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 – 3 tablets Levonorgestrel 30 µg (levonorgetrel 90 µg) Batch no. 3674F002C
Treatment R:	Reference – 3 tablets Norgeston® (levonorgestrel 90 µg) Batch no. 31018B

A 14 day wash-out period was observed between administration of test and reference. Serial blood samples (1 pre-dose sample and 20 samples within 72 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 analyzed using a validated LC-MS/MS method. The limit of quantification was stated to be about 0.051 ng/ml for levonorgestrel.

The study was performed with 14 participants; data generated from a total of 12 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} (h)#	1.0 (0.75 – 1.5)	1.125 (0.75 – 2.5)	-	-
C_{max} (ng/ml)	4.11 ± 1.97 (3.72)	4.28 ± 2.57 (3.65)	101.9	93.3 – 111.4
AUC_{0-72h} (ng.h/ml)	42.3 ± 25.1 (36.4)	43.3 ± 31.7 (35.8)	101.9	91.8 – 113.1

* geometric mean; # median (range)

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 Levonorgestrel 30 µg tablet meets the criteria for bioequivalence with regard to the rate and extent of absorption and is therefore bioequivalent to the reference Norgeston® (Bayer Plc.).

4. Summary of Product Safety and Efficacy

FAMY-POP has been shown to conform to the same relevant standards of quality, efficacy and safety as those required of the innovator product. FAMY-POP fulfilled all criteria for waiving an in-vivo bioequivalence study as per relevant WHO guidance.

The clinical safety of this product is considered to be acceptable when guidance and restrictions in the summary of product characteristics are taken into account. Reference is made to the Summary of Product Characteristics (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 FAMY-POP is used in accordance with the summary of product characteristics (SmPC).

Bioequivalence

FAMY-POP has been shown to be bioequivalent to the comparator product Norgeston® (Bayer Plc.).

Efficacy and Safety

Regarding clinical efficacy and safety, FAMY-POP is considered effective and safe to use when the guidance and restrictions in the SmPC are taken into consideration.

Benefit Risk Assessment

Based on the WHO's assessment of data on quality, bioequivalence, safety and efficacy the team of assessors considered that the benefit-risk profile of FAMY-POP was acceptable for contraception in women as detailed in the summary of product characteristics and has advised inclusion of FAMY-POP, manufactured at Jai Pharma Limited, Plot No. 20/21, Pharmez,The Pharmaceutical Special Economic Zone,Sarkhej - Bavla National Highway No-8A Nr. Village Matoda, Taluka-Sanand, Dist-Ahmedabad 382 213, Gujarat, India in the list of prequalified medicinal products.