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:	Zinnia P [*]
Manufacturer of Prequalified Product:	Famy Care Ltd. Unit II 1608/1609 G.I.D.C, Sarigam 396155 Valsad Gujarat, India
Active Pharmaceutical Ingredients (APIs):	Ethinylestradiol and levonorgestrel
Pharmaco-therapeutic group (ATC Code):	Progestogens and estrogens, fixed combinations (G03AA07)
Therapeutic indication:	Contraception for women

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

1. Introduction

Zinnia P is indicated for contraception for women.

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 ethinylestradiol and of levonorgestrel are supported by their respective EDQM Certificates of Suitability (CEPs). Both APIs are in micronized form and product appropriate specifications have been set for particle size distribution.

Other ingredients

Active tablets

Other ingredients used in the core tablet formulation include lactose monohydrate, maize starch, povidone, talc and magnesium stearate. The tablet coat contains povidone, talc, glycerol, sucrose, calcium carbonate, macrogol, titanium dioxide and carnauba wax.

Placebo tablets

Other ingredients used in the core placebo tablet formulation include lactose, maize starch, povidone, talc and magnesium stearate. The film-coating contains povidone, talc, glycerol, sucrose, calcium carbonate, macrogol, titanium dioxide, yellow oxide of iron and carnauba wax.

The excipients of the active and placebo tablets are all, with the exception of lactose and lactose monohydrate, of vegetable origin. TSE/BSE-free certifications have been provided for lactose and lactose monohydrate. Glycerol is routinely tested to demonstrate compliance with diethylene glycol test.

Finished pharmaceutical product (FPP)

Pharmaceutical development and manufacture

The active tablets containing 30 µg ethinylestradiol and 150 µg levonorgestrel are white, circular, biconvex, sugar coated tablets. The placebo tablets are yellow, circular, biconvex and sugar coated. The tablets are packaged in a clear transparent PVC/PVdC-Alu blister card, containing 21 active and seven placebo tablets.

The objective of the development programme was to formulate a robust, stable, acceptable formulation of the active tablets, comparable in performance to the reference product Microgynon® 30 (containing 30 µg ethinylestradiol and 150 µg levonorgestrel). The comparator product was characterized for physical and chemical properties in support of the development. The composition of the final formulation is essentially similar to that of the comparator product.

Particle size distribution of ethinylestradiol and of levonorgestrel has been identified as a critical quality attribute and is adequately controlled at the API stage. The manufacturing process of the core tablets entails direct compression. 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. Validation data presented for three primary batches demonstrated the consistency of the process and the quality of the product. The placebo tablets are manufactured in a similar way.

Product specifications

The specifications of the active tablets are regarded adequate for ensuring consistent quality thereof and include tests for description, identification of the APIs (HPLC and TLC) and of titanium dioxide, average weight, tablet dimensions, disintegration time, dissolution, uniformity of content, related substances (HPLC), assay of the actives (ethinylestradiol and levonorgestrel by HPLC), water content and microbial enumeration.

The specifications for the placebo tablets include tests for description, identification of titanium dioxide and yellow oxide of iron, average weight, tablet dimensions, disintegration time, absence of the actives (ethinylestradiol and levonorgestrel by HPLC), water content and microbial enumeration.

Stability testing

Stability studies have been conducted in at 30°C/65%RH as long-term storage conditions and for six months at accelerated conditions in the packaging proposed for marketing of the product. The active tablets proved to be quite stable at both conditions, showing a slight increase in ethinylestradiol degradation products with time. The placebo tablets proved to be stable over the period tested. 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.

A randomized, open label, two-sequence, two-treatment, two-period, crossover, single dose, bioequivalence study of fixed dose combination of Levonorgestrel 150µg and Ethinylestradiol 30 µg tablets of Famy Care Ltd. with Microgynon®30 (fixed dose combination of levonorgestrel 150µg and ethinylestradiol 30 µg tablets of Schering Pharma, in normal, healthy, adult, female human subjects under fasting condition (study no. ARL/08/008).

The objective of the study was to compare the bioavailability of the stated fixed dose combination Levonorgestrel/ethinylestradiol 150µg /30 µg tablets manufactured by Famy Care Ltd., India (test drug) with the same dose of the reference formulation (Microgynon®30 tablet, Schering Pharma) and to assess bioequivalence. The comparison was performed as a single centre, open label, randomised, crossover study in healthy subjects under fasting conditions. Each subject was assigned to receive each of the following two treatments:

Treatment T:	Test – 2xLevonorgestrel/ethinylestradiol 150µg /30 µg tablet (levonorgestrel 300µg + ethinylestradiol 60µg) Batch no. LE42P703.
Treatment R:	Reference – 2xMicrogynon®30 tablet (levonorgestrel 300µg + ethinylestradiol 60µg) Batch no. 62762A.

A 31 day wash-out period was observed between administration of test and reference. Serial blood samples (1 pre-dose sample and 25 samples within 168 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 and ethinylestradiol were analyzed using a validated LC-MS/MS method. The limit of quantification was stated to be about 0.30 ng/ml for levonorgestrel and about 20 pg/ml for ethinylestradiol.

The study was performed with 30 participants; data generated from a total of 28 subjects were utilized for analysis to establish pharmacokinetic parameters and assess bioequivalence.

Arithmetic mean and geometric mean values of the pharmacokinetic variables for levonorgestrel and ethinylestradiol as well as statistical results are summarised in the following table:

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)	1.7 ± 0.6	1.3 ± 0.3	-	-
C_{max} (ng/ml)	9.7 ± 3.6 (9.1)	11.6 ± 5.2 (10.5)	86.1	80.7 – 91.8
AUC_{0-t} (ng.h/ml)	145 ± 91 (123)	135 ± 65 (119)	103.5	97.1 – 110.4
AUC_{0-inf} (ng.h/ml)	166 ± 89 (147)	158 ± 62 (145)	100.9	96.1 – 106.0

* geometric mean

Ethinylestradiol

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)	1.7 ± 0.3	1.8 ± 0.4	-	-
C_{max} (pg/ml)	152 ± 49 (144)	157 ± 47 (150)	96.5	90.8 – 102.4
AUC_{0-t} (pg.h/ml)	1076 ± 504 (967)	1177 ± 834 (1000)	96.7	85.7 – 109.2
AUC_{0-inf} (pg.h/ml)	1498 ± 768 (1325)	1663 ± 1202 (1411)	93.9	83.1 – 106.1

* geometric mean

Conclusion

The results of the study show that preset acceptance limits of 80 -125 % are met by both AUC and C_{max} values regarding levonorgestrel and ethinylestradiol. Accordingly, the test fixed dose combination Levonorgestrel/ethinylestradiol 150µg /60µg tablets meets the criteria for bioequivalence with regard to rate and extent of absorption and is therefore bioequivalent to the reference Microgynon®30 tablet (Schering Pharma).

4. Summary of Product Safety and Efficacy

Zinnia P has been shown to conform to the same relevant standards of quality, efficacy and safety as those required of the innovator product. According to the submitted data on quality and bioavailability Zinnia P is pharmaceutically and therapeutically equivalent and thus interchangeable with the innovator product Microgynon® 30 tablets (fixed dose combination of levonorgestrel 150 µg and ethinylestradiol 30 µg) for which benefits have been proven in terms of clinical efficacy.

The clinical safety of this product is considered to be acceptable when guidance and restrictions as stated in the Summary of Product Characteristics are taken into account. Reference is made 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 Zinnia P is used in accordance with the SmPC.

Bioequivalence

Zinnia P has shown to be bioequivalent with Microgynon®30 tablets of Schering Pharma, Germany.

Efficacy and Safety

Regarding clinical efficacy and safety, Zinnia P is considered effective and safe to use when the guidance and restrictions in the Summary of Product Characteristics 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 Zinnia P was acceptable for the following indication: **"Contraception for women."** and has advised that the quality, efficacy and safety of Zinnia P allow inclusion of Zinnia P, manufactured at Famy Care Ltd. Unit II, 1608/1609, G.I.D.C, Sarigam, 396155 Valsad, Gujarat, India, in the list of prequalified medicinal products.