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	[RH035 trade name]*
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

1. Introduction

[RH035 trade name] is indicated in women for contraception.

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 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.

* Trade names are not prequalified by WHO. This is the national medicines regulatory authority's responsibility.
** Formerly known as Mylan Laboratories Limited

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.

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 150 µg and Ethinylestradiol 30 µg tablets of Famy Care Ltd. with Microgynon®30 (fixed dose combination of levonorgestrel 150 µg 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 150 µg /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 150 µg /30 µg tablet

(levonorgestrel 300 µg + ethinylestradiol 60 µg)
Batch no. LE42P703.

Treatment R: Reference – 2xMicrogynon®30 tablet

(levonorgestrel 300 µg + ethinylestradiol 60 µg)

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 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)	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

Ethinylestradiol

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)	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

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 150 µg /30 µg 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

[RH035 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, [RH035 trade name] is pharmaceutically and therapeutically equivalent and thus interchangeable with the comparator product Microgynon®30 tablet (Schering Pharma) for which benefits have been proven in terms of clinical efficacy. The clinical safety of [RH035 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 [RH035 trade name] is used in accordance with the SmPC.

Bioequivalence

[RH035 trade name] has been shown to be bioequivalent with Microgynon® (Schering Pharma).

Efficacy and Safety

Regarding clinical efficacy and safety, [RH035 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 [RH035 trade name] was acceptable for the following indication: '**Contraception for women** ', and would allow inclusion of [RH035 trade name], 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.