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	[RH093 trade name]*
Manufacturer of Prequalified Product	Renata Limited Rajendrapur Potent Product Facility, Noyapara, Bhawal Mirzapur, Rajendrapur, Gazipur 1700 Bangladesh
Active Pharmaceutical Ingredient(s) (API)	Ethinylestradiol/levonorgestrel
Pharmaco-therapeutic group (ATC Code)	Hormonal contraceptives: progestogens and estrogens, fixed combinations G03AA07
Therapeutic indication	[RH093 trade name] is indicated in women for contraception. It may also protect women against gynaecological conditions that respond to an oestrogen-progestogen combination.

1. Introduction

[RH093 trade name] is an oral combined hormonal contraceptive product containing ethinylestradiol (an oestrogen) and levonorgestrel (a progestogen).

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)

CEPs (Certificate of Suitability) issued by the EDQM were submitted, ensuring good manufacturing control and applicability of the Ph.Eur monograph to control quality of the APIs.

The FPP manufacturer's API specifications include particle size distribution which is regarded a critical quality attribute of both APIs. The acceptance criteria for this parameter were derived from the information of the API lots used in the FPP biobatch.

Stability testing was conducted according to the requirements of WHO. The proposed re-test periods are justified based on the stability results when the APIs are stored in the original packaging.

Other ingredients

Active tablets

* Trade names are not prequalified by WHO. This is the national medicines regulatory authority's responsibility.

Other ingredients used in the core tablet formulation include maize starch, pregelatinised starch, povidone, lactose monohydrate, magnesium stearate and colloidal anhydrous silica, all being pharmacopoeial controlled. The sugar-coating mixture contains polyvinyl alcohol-partially hydrolysed, titanium dioxide, talc, macrogol/ PEG, lecithin(soya), sucrose, acacia gum, maize starch, calcium carbonate, povidone, polysorbate, ferric oxide yellow and carnauba wax, all being controlled by acceptable specifications. Lactose monohydrate and magnesium stearate are of bovine and vegetable origin respectively. BSE/TSE compliance declarations were provided for all the excipients.

Placebo tablets

Other ingredients used in the core tablet formulation include microcrystalline cellulose, lactose monohydrate, colloidal anhydrous silica and magnesium stearate, all being pharmacopoeial controlled. The commercially sourced proprietary film-coating mixture contains polyvinyl alcohol-partially hydrolysed, titanium dioxide, talc, macrogol/ PEG and lecithin(soya) all being controlled by acceptable specifications. Lactose monohydrate and magnesium stearate are of bovine and vegetable origin respectively.BSE/TSE compliance declarations were provided for all the excipients.

Finished pharmaceutical product (FPP)

Pharmaceutical development and manufacture

The multisource product consists of active and placebo tablets, packaged in a clear plastic (PVC/PVDC) on aluminium foil blister card, each containing 21 active (yellow) tablets plus 7 placebo (white) tablets.

Active tablets

The active tablets are yellow, round, sugar-coated tablets. They are biconvex (rounded on top and bottom) with a round edge. The tablets are plain on both sides.

The objective of the formulation development was to obtain a product bioequivalent to the comparator product, Microgynon® 30. Based on the composition of the comparator product the manufacturer proceeded to use the same excipients in the tablet core with initially a film-coat. However, during the development it became apparent that a sugar-coated product may be more appropriate to meet the stability requirements for related substances for long term storage at 30^0C/75% RH. The ethinylestradiol /levonorgestrel 30 µg/150 µg tablets are low dose and one critical quality attribute is uniformity of content for the two actives. While the APIs were both micronized, the manufacturer's experience to achieve uniformity of content at these doses was to use the minimum quantity of methylene chloride and ethanol in the granulation solution. This achieves a "locking" of the APIs in place and allows an efficient distribution of the two APIs. The product showed consistency in the blend with respect to uniformity of content and assay and the tablets meeting the proposed finished product specification. Various experiments were performed to select and optimize the concentration of excipients and other process parameters to obtain tablets of desired characteristics. Satisfactory in-process controls have been established.

Placebo tablets

The placebo tablets are white, round, film-coated tablets. They are biconvex (rounded on top and bottom) with a flat edge. The tablets have "PO" debossed (stamped into) one side and "RO" on the other side.

The manufacturing process for the placebo tablets consists dispensing, blending, compression, coating, bulk packaging and blister packaging. Various experiments were performed to select and optimize the concentration of excipients and other process parameters to obtain tablets of desired characteristics. Satisfactory in-process controls have been established.

According to a risk evaluation by the applicant, the FPP appears to have no potential to contain nitrosamine impurities and hence no risk was identified.

Specifications

Active tablets

The finished product specifications include tests for appearance, identification of the APIs (TLC and HPLC), loss on drying, content uniformity (uniformity of dosage units), assay (HPLC), dissolution (HPLC detection), related substances (HPLC), residual solvents (GC) and microbial limits.

Placebo tablets

The finished product specifications include tests for appearance, loss on drying, assay (absence of APIs), hardness, disintegration, average weight, and microbial limits.

Stability testing

Stability studies have been conducted at 30°C/75% RH as long-term storage condition and for six months at accelerated conditions in the packaging intended for marketing of the product. The data provided show that the product is stable at these storage conditions. 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 2023 according to internationally accepted guidelines.

An open label, balanced, randomized, two treatments, two sequence, two period, single oral dose, crossover, bioequivalence study of levonorgestrel/ethinylestradiol 0.15 mg/0.03 mg sugar coated tablet in healthy, adult, human female subjects under fasting condition (study no. 0055-23).

The objective of the study was to compare the bioavailability of the stated levonorgestrel/ethinylestradiol 0.15/0.03 mg FDC tablet manufactured by/for Renata Ld., Bangladesh (test drug) with the reference formulation Microgynon® 30 (Bayer AG) 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 two treatments in a randomized fashion:

Treatment T:	Test – 1 tablet Levonorgestrel/Ethinylestradiol 0.15/0.03 mg (levonorgestrel 0.15 mg + ethinylestradiol 0.03 mg) Batch no. K0221002.
Treatment R:	Reference – 1 tablet Microgynon® 30 (ethinylestradiol 0.03 mg + levonorgestrel 0.15 mg) Batch no. KT0F21J.

A 21 day wash-out period was observed between administration of test and references. Serial blood samples (1 pre-dose sample and 18 samples within 72 h post dose) were taken during each study period to obtain bioavailability characteristics AUC, Cmax and tmax for bioequivalence evaluation. Drug concentrations for ethinylestradiol and levonorgestrel were analyzed using validated LC-MS/MS methods. The limit of quantification was stated to be about 2 pg/mL for ethinylestradiol and 50 pg/mL for levonorgestrel.

The study was performed with 42 participants; data generated from a total of 41 subjects were utilized for analysis to establish pharmacokinetic parameters and assess bioequivalence.

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

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)	1.50 (1.00 – 2.50)	1.75 (1.00 – 2.75)	–	–
C_{max} (pg /mL)	84.3 ± 31.5 (79.0)	79.8 ± 28.9 (75.2)	105.0	100.4 – 109.9
AUC_{0-t} (pg ·h/mL)	889 ± 335 (832)	863 ± 360 (797)	104.4	100.5 – 108.6

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)	1.00 (0.72 – 1.75)	1.01 (0.50 -2.75)	–	–
C_{max} (ng /mL)	4.11 ± 1.76 (3.80)	4.30 ± 1.90 (3.98)	95.4	86.6 – 105.0
AUC_{0-72h} (ng·h/mL)	47.1 ± 22.1 (42.5)	52.1 ± 35.9 (45.2)	93.9	85.1 – 103.6

4. Summary of product safety and efficacy

[RH093 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, [RH093 trade name] is pharmaceutically and therapeutically equivalent and thus interchangeable with the comparator product Microgynon® 30 (Bayer AG) for which benefits have been proven in terms of clinical efficacy. The clinical safety of [RH093 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 [RH093 trade name] is used in accordance with the SmPC.

Bioequivalence

[RH093 trade name] has been shown to be bioequivalent with Microgynon® 30 (Bayer AG).

Efficacy and Safety

Regarding clinical efficacy and safety, [RH093 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 [RH093 trade name] was acceptable for the following indication: 'in women for contraception' and would allow inclusion of [RH093 trade name], manufactured at Renata Limited, Rajendrapur Potent Product Facility, Noyapara, Bhawal Mirzapur, Rajendrapur, Gazipur 1700, Bangladesh in the list of prequalified medicinal products.