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	[RH068 trade name][*]
Manufacturer of Prequalified Product	Laboratorios Leon Farma SA
Active Pharmaceutical Ingredient(s) (API)	Levonorgestrel
Pharmaco-therapeutic group (ATC Code)	Sex hormones and modulators of the genital system, emergency contraceptives (G03AD01)
Therapeutic indication	[RH068 trade name] is an emergency contraception for women.

1. Introduction

[RH068 trade name] is an emergency contraceptive agent for women.

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 Ingredients (APIs)

A CEP (Certificate of Suitability) issued by the EDQM was submitted, ensuring good manufacturing control and applicability of the Ph.Eur monograph to control quality of the API.

The FPP manufacturer's API specifications include particle size distribution which is regarded a critical quality attribute of levonorgestrel. 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 period is justified based on the stability results when the API is stored in the original packaging.

Other ingredients

Other ingredients used in the tablet formulation include microcrystalline cellulose, lactose monohydrate, poloxamer, croscarmellose sodium and magnesium stearate, all being pharmacopoeial controlled. BSE/TSE compliance declarations were provided for all the excipients.

Finished pharmaceutical product (FPP)

Pharmaceutical development and manufacture

The multisource product is a white, round, biconvex tablet engraved with 'C' on one side and '2' on the other side. The tablets are packaged in a clear to slightly opaque PVC/PVdC-aluminium blister. Each blister card contains 2 tablets.

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

Two Levonorgestrel tablet strengths, proportional in composition (the only difference is the amount of lactose monohydrate, which is less in the case of levonorgestrel 1.5mg tablets to compensate for the quantity of the active pharmaceutical ingredient), were developed: 0.75mg and 1.5mg. The development focussed on the lower strength and once the formula was optimized, it was scaled up for the higher strength.

The objective of the formulation development was to obtain a product bioequivalent to the WHO recommended comparator product, Postinor®, and feasible to be manufactured. The study of the excipients of the comparator product suggested wet granulation as the most probable manufacturing method. However direct compression manufacturing process was tried and selected to simplify the process. It was concluded that a key point of the method of the manufacture was the use of micronized levonorgestrel and the inclusion of a disintegrant and a wetting agent in the formulation. For this very low dose, high potency product, critical issues regarding blend and content uniformity were addressed via the control strategy of the manufacturer. 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.

Specifications

The finished product specifications include tests for appearance, identification of the API (HPLC and UV), assay (HPLC), water content (KF), dissolution (HPLC detection), content uniformity (uniformity of dosage units), related substances (HPLC) and microbial limits.

Stability testing

Stability studies have been conducted at 25°C/65%RH, 30°C/65%RH and 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 Bio-Equivalence

A biowaiver was granted for [RH068 trade name], the additional 0.75 mg tablet strength (Laboratorios Leon Farma, S.A.) in accordance to WHO guideline. In comparison with the strength of the test product used in the bioequivalence study, the [RH068 trade name] was determined to be qualitatively essentially the same, the ratio of active ingredient and excipients between the strengths was considered essentially the same and the dissolution profiles between the formulations for the APIs were determined the same.

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

A randomized, 2-way crossover, single dose study to assess the bioequivalence of a new formulation of Levonorgestrel 1.5 mg / Laboratorios Leon Farma, S.A. versus Postinor® 1.5 mg / Schering GmbH und Co. Produktions kg in healthy volunteers under fasting state (study no. LVE-P0-757).

The objective of the study was to compare the bioavailability of the stated Levonorgestrel 1.5 mg tablet manufactured by/for Laboratorios Leon Farma, S.A. (test drug) with the reference formulation Postinor® (Schering GmbH) 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 1.5 mg (levonorgestrel 1.5 mg) Batch no. LFD0145A.

Treatment R: Reference – 1 tablet Postinor® 1.5 mg (levonorgestrel 1.5 mg) Batch no. WEF1WK.

A 28 day wash-out period was observed between administration of test and reference. Serial blood samples (1 pre-dose sample and 19 samples within 72h 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 0.25 ng/ml for levonorgestrel.

The study was performed with 40 participants; data generated from a total of 39 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 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)	2.0 ± 0.9	1.75 ± 0.7	-	-
C_{max} (ng/ml)	19.5 ± 5.8 (18.7)	22.4 ± 6.6 (21.4)	87.3	83.5 – 91.2
AUC_{0-t} (ng.h/ml)	282 ± 124 (257)	285 ± 125 (257)	100.0	94.3 – 106.0
AUC_{0-inf} (ng.h/ml)	315 ± 133 --	320 ± 137 --	-	-

*geometric mean

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 1.5 mg tablet meets the criteria for bioequivalence with regard to the rate and extent of absorption and is therefore bioequivalent to the reference Postinor® 1.5 mg (Schering GmbH).

4. Summary of product safety and efficacy

According to the submitted data on quality [RH068 trade name] is a direct scale-down of [RH069 trade name]. The latter is pharmaceutically and therapeutically equivalent and thus interchangeable with the comparator product, for which benefits have been proven in terms of efficacy.

The clinical safety of [RH068 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.

2. 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 [RH068 trade name] is used in accordance with the SmPC.

Bioequivalence

[RH068 trade name] fulfilled all criteria for waiving an in-vivo bioequivalence study as per relevant WHO guidance.

Efficacy and Safety

Regarding clinical efficacy and safety, [RH068 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 [RH068 trade name] was acceptable for the following indication: emergency contraception within 72 hours of unprotected sexual intercourse or failure of a contraceptive method and would allow inclusion of [RH068 trade name] , manufactured at Laboratorios Leon Farma SA, C/La Vallina s/n, Poligono Industrial Navatejera, Villaquilambre, Leon 24008, Spain, in the list of prequalified medicinal products.