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	[RH052 trade name] *
Manufacturer of Prequalified Product	China Resources Zizhu Pharmaceutical Co., Ltd. No. 27, Chaoyang North Road Chaoyang District, Beijing 100024 P. R. China
Active Pharmaceutical Ingredient (API)	mifepristone
Pharmaco-therapeutic group (ATC Code)	Progesterone Receptor Modulators (G03XB01)
Therapeutic indication	Medical termination of developing intrauterine pregnancy, softening and dilatation of the cervix uteri prior to surgical termination of pregnancy during the first trimester and preparation for the action of prostaglandin analogues in the termination of pregnancy for medical reasons.

1. Introduction

[RH052 trade name] is indicated for medical termination of developing intra-uetrine pregnancy, softening and dilatation of the cervix uteri prior to surgical termination of pregnancy during the first trimester and preparation for the action of prostaglandin analogues in the termination of pregnancy for medical reasons.

[RH052 trade name] should be prescribed and administered in accordance with countries' national laws and regulations.

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)

Mifepristone (micronized) used in the manufacture of Mifepristone 200 mg Tablets has been prequalified by WHO according to WHO's Procedure for assessing the acceptability, in principle, of active pharmaceutical ingredients for use in pharmaceutical products (WHO Technical Report Series No. 953, 2009, Annex 4). This procedure provides an assurance that mifepristone, used in the manufacture of Mifepristone 200 mg Tablets, is of good quality and manufactured in accordance with WHO good manufacturing practices (GMP). API prequalification consists of a comprehensive

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

evaluation procedure that has two components: Assessment of the API master file (APIMF) to verify compliance with WHO norms and standards, and assessment of the sites of API manufacture to verify compliance with WHO GMP requirements.

The API is of BCS low solubility, hence particle size distribution and polymorphism are considered critical parameters. The API supplier produces polymorphic Form I. Micronized mifepristone is used in the manufacture of the FPP.

Other ingredients

Other ingredients used in the tablet formulation include corn starch, microcrystalline cellulose, povidone, colloidal silicon dioxide and magnesium stearate. None of the excipients are derived from human or animal sources.

Finished pharmaceutical product (FPP)

Pharmaceutical development and manufacture

The multisource product is a yellowish, biconvex tablet, debossed with M1 on one side; the other side is plain. The tablets are presented in PVC-Al blister packs.

The objective of the manufacturer was to develop a stable immediate release tablet, with acceptable characteristics, that would be bioequivalent to the WHO PQTm comparator product, Mifegyne® 200 mg tablets. Following an analysis of the comparator product, a quality target product profile (QTPP) was defined for the multisource product. The composition of the final formulation is qualitatively similar to that of the comparator product. In addition, compatibility studies were conducted between API and proposed excipients which showed that they are compatible. The formula was finalised after a series of formulation optimization studies.

Wet granulation resulted in satisfactory tabletting parameters and similar dissolution profiles to that of the comparator product. Hence the wet granulation method was selected for product development and further optimized. Appropriate in-process controls were set to ensure batch-to-batch reproducibility.

Specifications

The product specifications include tests for tablet description, identification of API (HPLC, UV), related substances (HPLC), dissolution (HPLC detection), weight variation, loss on drying, assay (HPLC) and microbial limits. The analytical procedures have been adequately validated.

Stability testing

Stability studies have been performed at 30°C/75%RH (zone IVb) as long-term storage conditions and for six months at accelerated conditions in the packaging proposed for marketing of the product. The product proved to be quite stable at these storage conditions and showed only slight increase in degradation products, though within justified limits. Based on the available stability data, the proposed shelf life and storage conditions of the FPP 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 2013 according to internationally accepted guidelines.

A randomized, open label, two treatment, two period, two sequence, single dose, crossover, bioequivalence study of Mifepristone 200 mg tablets of China Resources Zizhu Pharmaceutical Co., Ltd., P.R. China and Mifegyne® (mifepristone) 200 mg tablets of Exelgyn, France, in healthy human adult male subjects, under fasting conditions (study no. 2719/12).

The objective of the study was to compare the bioavailability of the stated Mifepristone 200 mg tablets manufactured by China Resources Zizhu Pharmaceutical Co., Ltd., P.R. China (test drug) with the reference formulation Mifegyne® (Exelgyn) 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 Mifepristone 200 mg
(mifepristone 200 mg)
Batch no. 45130401.

Treatment R: Reference – 1 tablet Mifegyne®
(mifepristone 200 mg)
Batch no. 11071.

A 19 day wash-out period was observed between administration of test and reference. Serial blood samples (1 pre-dose sample and 24 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 mifepristone were analyzed using a validated LC-MS/MS method. The limit of quantification was stated to be about 17 ng/mL for mifepristone.

The study was performed with 84 participants; data generated from a total of 76 subjects were utilized for analysis to establish pharmacokinetic parameters and assess bioequivalence.

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

Mifepristone

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)	1.47 ± 2.70	1.69 ± 3.73	–	–
C_{max} (µg /mL)	2.32 ± 0.85 (2.19)	2.20 ± 0.70 (2.09)	104.7	96.1 – 114.1
AUC_{0-t} (µg·h/mL)	42.3 ± 17.5 (39.0)	41.1 ± 15.9 (38.0)	102.8	96.3 – 109.6

The results of the study show that preset acceptance limits of 80 -125 % are met by both AUC and Cmax values regarding mifepristone. Accordingly, the test tablet Mifepristone 200 mg meets the criteria for bioequivalence with regard to the rate and extent of absorption and is therefore bioequivalent to the reference Mifegyne® (Exelgyn).

4. Summary of product safety and efficacy

[RH052 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, [RH052 trade name] is pharmaceutically and therapeutically equivalent and thus interchangeable with the comparator product Mifegyne® tablets for which benefits have been proven in terms of clinical efficacy.

The clinical safety of [RH052 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 [RH052 trade name] is used in accordance with the SmPC.

Bioequivalence

[RH052 trade name] has been shown to be bioequivalent with Mifegyne tablets of Exelgyn, France.

Efficacy and Safety

Regarding clinical efficacy and safety, [RH052 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 [RH052 trade name] was acceptable for the following indication: 'medical termination of developing intra-uterine pregnancy, softening and dilatation of the cervix uteri prior to surgical termination of pregnancy during the first trimester and preparation for the action of prostaglandin analogues in the termination of pregnancy for medical reasons', and would allow inclusion of [RH052 trade name], manufactured at China Resources Zizhu Pharmaceutical Co., Ltd., No. 27, Chaoyang North Road, Chaoyang District, Beijing 100024, P. R. China in the list of prequalified medicinal products.