

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	[RH056 trade name]*
Manufacturer of Prequalified Product	ACME Formulation Pvt. Limited (Hormone Block) Ropar Road, Nalagarh Dist. Solan Himachal Pradesh-174101 India
Active Pharmaceutical Ingredient(s) (API)	Misoprostol
Pharmaco-therapeutic group (ATC Code)	Uterotonics, Prostaglandins (G02AD06)
Therapeutic indication	Prevention of post partum haemorrhage when oxytocin is not available, induction of labour, incomplete abortion as well as spontaneous and induced abortion (preferably with mifepristone)

1. Introduction

[RH056 trade name] is indicated for prevention of postpartum haemorrhage when oxytocin is not available, for induction of labour and for spontaneous and induced abortion (preferably with mifepristone).

[RH056 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)

Misoprostol Dispersion (1:100 in HPMC) used in the manufacture of Misoprostol 200µg 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 Misoprostol

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

Dispersion (1:100 in HPMC), used in the manufacture of Misoprostol 200µg Tablets, is of good quality and manufactured in accordance with WHO good manufacturing practices (GMP).

API prequalification consists of a comprehensive 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

Other ingredients

Other ingredients used in the tablet formulation include microcrystalline cellulose, sodium starch glycolate, hydrogenated castor oil and hypromellose (HPMC). None of the excipients are derived from human or animal sources.

Finished pharmaceutical product (FPP)

Pharmaceutical development and manufacture

The multisource product is a white to off white, round, biconvex, uncoated tablet, plain on both sides. The tablets are presented in cold form aluminium (Alu-Alu) blister packs. Each tablet contains 200 µg misoprostol as a 1:100 dispersion in HPMC.

The objective of the manufacturer was to develop an immediate release tablet that would be bioequivalent to the WHO PQTm comparator product, Cytotec® 200 µg tablets. The comparator product was characterized for physical and chemical properties in support of the development. The composition of the final formulation is qualitatively similar to that of the comparator product. The manufacturing process entails direct compression. Optimization studies included targeting of the dissolution profiles of the comparator product. The primary packaging (Alu-Alu) has been selected for protection of the tablet against moisture. Appropriate in-process controls were set to ensure batch-to-batch reproducibility.

Specifications

The product specifications include tests for appearance, identification of API (HPLC, UV), uniformity of mass, moisture content, disintegration time, uniformity of dosage units (by content uniformity), assay (HPLC) dissolution (by HPLC), related impurities (HPLC) and microbial enumeration. 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 is chemically not very stable; the data showed an increase of degradation products with time at accelerated and long term storage conditions, 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 2014 according to internationally accepted guidelines.

Study Title: A randomized, open label, balanced, two-treatment, two-period, two-sequence, single dose, crossover, bioequivalence study of Misoprostol (misoprostol) 200 µg tablet of ACME Formulation Pvt. Ltd., India with Cytotec 200 µg misoprostol tablets of Pharmacia Ltd, UK in normal, healthy, adult, female human subjects under non fasting condition (study no. ARL/13/679).

The objective of the study was to compare the bioavailability of the stated Misoprostol 200 µg tablet manufactured for/by ACME Formulation Pvt. Ltd., India (test formulation) with the reference formulation Cytotec® (Pharmacia Ltd,) and to assess bioequivalence. The comparison was performed as a single centre, open label, randomized, crossover study in healthy subjects under fed conditions. Each subject was assigned to receive each of the following treatments in a randomized fashion:

Treatment T: Test – 2 tablets [RH056 trade name]
(misoprostol 400 µg)
Batch no. ACMAK4001.

Treatment R: Reference – 2 tablets Cytotec®
(misoprostol 400 µg)
Batch no. B04370

An 11 day wash-out period was observed between administration of test and reference. Serial blood samples (1 pre-dose sample and 19 samples within 10 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 misoprostol acid were analyzed using a validated LC-MS/MS method. The limit of quantification was stated to be about 15 pg/mL for misoprostol acid.

The study was performed with 46 participants; data generated from a total of 45 subjects were utilized for analysis to establish pharmacokinetic parameters and assess bioequivalence.

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

Misoprostol acid

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)	2.00 ± 0.87	1.63 ± 1.01	–	–
C _{max} (pg /mL)	419 ± 142 (396)	442 ± 173 (413)	95.8	88.9 – 103.2
AUC _{0-t} (pg·h/mL)	1009 ± 325 (965)	985 ± 316 (934)	103.3	98.1 – 108.9
AUC _{0-inf} (pg·h/mL)	1075 ± 318 (--)	1014 ± 313 (--)	n.c	n.c

n.c.: not calculated

The results of the study show that preset acceptance limits of 80 -125 % are met by both AUC and C_{max} values regarding misoprostol acid. Accordingly, the test tablet Misoprostol 200 µg meets the criteria for bioequivalence with regard to the rate and extent of absorption and is therefore bioequivalent to the reference Cytotec® (Pharmacia Ltd, UK).

4. Summary of product safety and efficacy

[RH056 trade name] 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 [RH056 trade name] is pharmaceutically and therapeutically equivalent and thus interchangeable with the innovator product Cytotec® tablets 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 [RH056 trade name] is used in accordance with the SmPC.

Bioequivalence

[RH056 trade name] has been shown to be bioequivalent with Cytotec tablets of Pharmacia Ltd, UK.

Efficacy and Safety

Regarding clinical efficacy and safety, [RH056 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 [RH056 trade name] was acceptable for the following indication: **Prevention of postpartum haemorrhage when oxytocin is not available, for induction of labour, for incomplete abortion as well as spontaneous and induced abortion (preferably with mifepristone** , and would allow inclusion of [RH056 trade name], manufactured at in the list of prequalified medicinal products.