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	[RH039 trade name][*]
Manufacturer of Prequalified Product	Cipla Limited (Cipla Goa, unit 8) L-147 to L-147/1 L-147-3 to L-138 Verna Industrial Estate, Verna Goa. 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, for induction of labour and for spontaneous and induced abortion (preferably with mifepristone).

1. Introduction

[RH039 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). [See Part 4 Summary of Products Characteristics (SmPC), for full indications].

[RH039 trade name] should be prescribed and administered in accordance with countries' national laws and regulations.

2. Assessment of quality

The assessment was done according to SOP 20 of the WHO Prequalification Programme.

Active pharmaceutical Ingredient (API)

Misoprostol is a clear, colourless to yellowish, hygroscopic oily liquid. The molecule contains four stereogenic carbon centres and the substance is produced in multiple steps as a mixture of four stereo-isomers (see e.g. the Ph.Eur.) in about equal proportions. Misoprostol is pharmacopoeial controlled. It is stored at -20ºC due to its poor stability.

Misoprostol is supplied as misoprostol-HPMC 1% dispersion. The dispersion shows enhanced stability properties for misoprostol and is prepared utilising an organic solvent in which misoprostol is soluble. Misoprostol is uniformly distributed in misoprostol-HPMC 1% dispersion as demonstrated by validation data.

Misoprostol-HPMC 1% dispersion is adequately controlled by its specifications which include tests for appearance, identification (HPLC and UV), solubility, water content, heavy metals, related compounds (HPLC), assay (HPLC), particle size and residual solvents.

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

Stability testing was conducted according to the requirements of WHO. The proposed shelf life is justified based on the stability results when the dispersion is stored at refrigerated conditions in the original packaging.

Other ingredients

Other ingredients include microcrystalline cellulose, sodium starch glycolate and hydrogenated castor oil. It has been declared that the excipients used for manufacturing of the finished product are TSE/BSE risk free.

Finished Pharmaceutical Product (FPP)

Pharmaceutical development and manufacture

The product is a white to off-white capsule shaped, biconvex, uncoated tablet plain on both the sides. The tablets are packaged in Alu/Alu blisters for protection against moisture.

The objective of the manufacturer was to develop an immediate release tablet that would be bioequivalent to the comparator product, Cytotec® 200 tablets. The selection of the excipients was based on the composition of the comparator product, functional properties and compatibility with misoprostol-HPMC 1% dispersion. The particle size of the filler is controlled by the manufacturer to ensure proper distribution of the API in the blend.

The manufacturing process consists of more than one blending step, followed by compression and packaging of the tablets. Appropriate in-process controls were set to ensure batch-to-batch reproducibility. The biobatch showed very rapid dissolution properties, similar to the comparator product.

Product specifications

The finished product specifications are regarded adequate for ensuring consistent quality and include tests for description, identification of the API (HPLC and UV), average weight and weight variation, hardness, friability, disintegration time, water content, uniformity of dosage units (by content uniformity), dissolution (HPLC detection), assay (HPLC), degradation products (HPLC) and microbiological examination of non-sterile products. Batch analysis data confirmed consistency and uniformity of manufacture and indicated that the process is under control.

Stability testing

Stability studies have been conducted at 30°C/75%RH as long-term storage conditions and for 6 months at accelerated conditions in the packaging intended 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. The stability of the preparation for administration of a fractional dose as described in the SmPC/PIL is supported by in-use studies.

Conclusion

The quality part of the dossier is accepted.

3. Assessment of bioequivalence

The following bioequivalence study has been performed in 2012 according to internationally accepted guidelines:

A randomized, balanced, open label, two-sequence, two-treatment, four-period, single dose, replicate crossover, bioequivalence study of Misoprostol 200 µg tablets of Cipla Ltd., India, with Cytotec® (misoprostol 200 µg) tablets of Pharmacia Ltd., UK, in normal, healthy, adult, male human subjects under fed conditions (study no. ARL/11/104).

The objective of the study was to compare the bioavailability of the stated Misoprostol 200 µg tablet manufactured by Cipla Ltd., India (test drug) with the same dose of the reference formulation (Cytotec®,

Pharmacia Ltd.) and to assess bioequivalence. The comparison was performed as a single centre, open label, randomized, replicate, crossover study in healthy male subjects under fed conditions. Each subject was assigned to receive each of the following two treatments in a randomized fashion:

Treatment T: Test – 1 tablet [RH039 trade name]
(misoprostol 200 µg)
Batch no. X15913
Treatment R: Reference – 1 tablet Cytotec®
(misoprostol 200 µg)
Batch no. A02463

A wash-out period of at least 3 days was observed between the 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 5 pg/ml.

The study was performed with 36 participants; data generated from a total of 36 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 tables:

Misoprostol acid

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)	1.57 ± 0.99	1.36 ± 0.93	-	-
C_{max} (pg/ml)	242 ± 135 (220)	247 ± 96 (233)	94.8	85.6 – 104.9
AUC_{0-t} (pg.h/ml)	520 ± 154 (509)	521 ± 164 (518)	99.5	96.1 – 102.9
AUC_{0-inf} (pg.h/ml)	534 ± 154 (494)	540 ± 159 (496)	98.2	94.9 – 101.6

* 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 misoprostol acid. Accordingly, the test tablet [RH039 trade name] meets the criteria for bioequivalence with regard to the rate and extent of absorption and is therefore bioequivalent to the reference Cytotec® (Pharmacia Ltd.).

4. Summary of product safety and efficacy

[RH039 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, [RH039 trade name] is pharmaceutically and therapeutically equivalent and thus interchangeable with the comparator products Cytotec® 200 µg tablet for which benefits have been proven in terms of clinical efficacy. The clinical safety of [RH039 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 [RH039 trade name] is used in accordance with the SmPC.

Biowaiver

[RH039 trade name] has been shown to have similar dissolution characteristics with Cytotec® 200 µg tablet (Pharmacia Ltd, UK).

Efficacy and Safety

Regarding clinical efficacy and safety, [RH039 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 the WHO's assessment of data on quality, bioequivalence, safety and efficacy the team of assessors considered that the benefit-risk profile of [RH039 trade name] was acceptable for the following indications: **"Prevention of postpartum haemorrhage when oxytocin is not available, for induction of labour and for spontaneous and induced abortion (preferably with mifepristone)."** and has advised to include [RH039 trade name], manufactured at Cipla Limited, L-147 to L-147-1, L-147-3 to L-138, Unit VIII, Verna Industrial Estate, Goa 403722, India in the list of prequalified medicinal products.