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	[RH094 trade name]*
Manufacturer of Prequalified Product	Mylan Laboratories Limited Plot No: 20 & 21, Pharmez, Sarkhej-Bavla, National Highway No. 8A, Near Village Matoda, Tal.-Sanand, Dist.-Ahmedabad - 382 213. Gujarat, India
Active Pharmaceutical Ingredient(s) (API)	Misoprostol
Pharmaco-therapeutic group (ATC Code)	Uterotonics, Prostaglandins (G02AD06)
Therapeutic indication	[RH094 trade name] is indicated for induction of labour, prevention of postpartum haemorrhage, induction of abortion (alone in combination with mifepristone or letrozole) and management of incomplete abortion or missed abortion & intrauterine fetal death (alone or in combination with mifepristone).

1. Introduction

[RH094 trade name] is indicated for induction of labour at term or in the third trimester of pregnancy after death of the fetus or where there is a fetal anomaly.

[RH094 trade name] is also indicated for prevention of postpartum haemorrhage when oxytocin is not available. It is also used in combination with mifepristone or letrozole, or used alone, for the induction of abortion. It may also be used alone for cervical priming before surgical abortion.

[RH094 trade name] is also used for incomplete abortion, and with mifepristone or alone for the management of missed abortion and intrauterine fetal death. [See Part 4 Summary of Products Characteristics (SmPC), for full indications].

[RH094 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 (HPMC 1% dispersion) 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 the API, used in the manufacture of [RH094 trade name], is of good quality

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

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 and hydrogenated castor oil. TSE/BSE free certificates from the suppliers have been provided with regard to all the excipients. 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 uncoated, capsule shaped, biconvex, bevelled edge tablet, debossed with "M" on one side and "I" on the other side. Each tablet contains 200 mcg misoprostol as a 1% dispersion in HPMC. The tablets are packaged in Alu/Alu blisters.

The objective of this development was to formulate an immediate release tablet that would be bioequivalent to the WHO PQTm recommended comparator product, Cytotec® (misoprostol 200 mcg) tablets. The selection of the excipients was primarily based on the qualitative composition of the comparator product, API-excipient compatibility studies and prior experience in manufacturing similar types of solid oral immediate release dosage forms. Based on the physicochemical properties of the API and its low dose in the formulation, direct compression manufacturing process was selected for the FPP. Various experiments were performed to select and optimize the concentration of excipients and other process parameters to obtain tablets of desired characteristics, including dissolution profile similarity with the comparator product. 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

The product specifications include tests for tablet description, identification of API (HPLC, UV), dissolution (by HPLC detection), uniformity of dosage units (by content uniformity), related substances (HPLC), assay (HPLC), water content (KF) 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. 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

No bioequivalence study has been performed. As misoprostol is selected by the WHO being eligible for a BCS based biowaiver, a request for a biowaiver has been made. In accordance with the WHO guidance and criteria for biowaivers, supporting data have been provided regarding formulation comparability and in vitro dissolution data.

Comparability between the reference Cytotec® 200 µg tablet (Pfizer) and the test Misoprostol 200 µg tablet (Mylan Laboratories Ltd.) regarding the qualitative and quantitative composition of the formulations have been sufficiently proven. In addition, comparable in vitro dissolution at a pH 1.2,

4.5 and 6.8 have been shown. Accordingly, the test tablet Misoprostol 200 µg tablet (Mylan Laboratories Ltd.) meets the criteria for a BCS based biowaiver and is therefore considered bioequivalent to the respective reference Cytotec® 200 µg tablet (Pfizer).

4. Summary of product safety and efficacy

[RH094 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, [RH094 trade name] is pharmaceutically and therapeutically equivalent and thus interchangeable with the comparator products Cytotec® 200 µg tablet (Pfizer) for which benefits have been proven in terms of clinical efficacy. The clinical safety of [RH094 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 [RH094 trade name] is used in accordance with the SmPC.

Biowaiver

[RH094 trade name] has been shown to have similar dissolution characteristics with Cytotec® 200 µg tablet (Pfizer).

Efficacy and Safety

Regarding clinical efficacy and safety, [RH094 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 [RH094 trade name] was acceptable for the following indications: **'for induction of labour, prevention of postpartum haemorrhage, induction of abortion (alone in combination with mifepristone or letrozole) and management of incomplete abortion or missed abortion & intrauterine fetal death (alone or in combination with mifepristone).'**, and would allow inclusion of [RH094 trade name], manufactured at Mylan Laboratories Limited, Plot No: 20 & 21, Pharmez, Sarkhej-Bavla, National Highway No. 8A, Near Village Matoda, Tal.-Sanand, Dist.-Ahmedabad - 382 213, Gujarat, India in the list of prequalified medicinal products.