This part reflects the scientific knowledge and the information about this product available at the time of prequalification. Thereafter, updates may have become necessary, which are included in parts 1 to 5 and, if related to pharmaceutical issues also documented in part 8 of this WHOPAR.

SCIENTIFIC DISCUSSION

Name of the Finished Pharmaceutical Product:	Rifampicin/Isoniazid/Pyrazinamide 75mg/50mg/150mg Dispersible Tablets [1]
Manufacturer of Prequalified Product:	Macleods Pharmaceuticals Limited Phase II, Unit II Plot No 25-27, Survey No 366 Premier Industrial Estate Kachigam, Daman, 369 210 India
Active Pharmaceutical Ingredients (APIs):	Rifampicin, Isoniazid, Pyrazinamide
Pharmaco-therapeutic group (ATC Code):	Antimycobacterials, combinations of drugs for treatment of tuberculosis (J04AM05)
Therapeutic indication:	Rifampicin/Isoniazid/Pyrazinamide 75mg/50mg/150mg Dispersible Tablets is indicated for the treatment of tuberculosis in children, caused by drug-susceptible *Mycobacterium tuberculosis*.

[1]Trade names are not prequalified by WHO. This is the national medicines regulatory authority's (NMRA) responsibility. Throughout this WHOPAR the proprietary name is given as an example only.

1. Introduction

Rifampicin/Isoniazid/Pyrazinamide 75mg/50mg/150mg Dispersible Tablets is indicated in children weighing between 4 kg and 24 kg for the initial treatment of tuberculosis, caused by drug-susceptible *Mycobacterium tuberculosis*.

Rifampicin/Isoniazid/Pyrazinamide 75mg/50mg/150mg Dispersible Tablets should be initiated by a health care provider experienced in the management of tuberculosis infection.

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

Rifampicin

Rifampicin API is described in the Ph.Int, Ph.Eur and the USP, and is considered well-established in the WHO Prequalification Team – Medicines (PQTm) programme. Compacted rifampicin is used in the manufacture of the dispersible tablets.

The API specifications are pharmacopoeial based and include tests for description, solubility, identification of the API and of its crystal form (XRPD), pH, loss on drying, heavy metals, sulfated ash, related substances (HPLC), assay (UV/HPLC), crystallinity, bulk density residual solvents (GC) and particle size distribution.

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 packing material.

Isoniazid

Based on scientific principles WHO PQTm has identified isoniazid up to 300 mg oral dose as a BCS class 3 API. The API is thus regarded highly soluble in terms of the BCS.

Isoniazid is described in the Ph.Int, Ph.Eur and USP and is considered well-established in WHO PQTm.

The API specifications, which are pharmacopoeial based, include tests for description, solubility, identification (m.p., IR), appearance and pH of solution, hydrazine and related substances (TLC/HPLC), heavy metals, loss on drying, sulfated ash, assay (titrimetric/HPLC), related substances (HPLC), residual solvents (GC), manganese (AAS), other metal impurities (molybdenum, nickel, chromium and vanadium with ICPMS) and particle size.

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 packing material.

Pyrazinamide

Based on scientific principles, WHO PQTm has identified pyrazinamide up to 500 mg oral dose as a BCS class 3 API. The API is thus regarded as highly soluble in terms of the BCS.

Pyrazinamide has been prequalified by WHO PQTm 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 pyrazinamide, used in the manufacture of the dispersible 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 tablet formulation include microcrystalline cellulose, crospovidone, povidone, bleached shellac, croscarmellose sodium, aspartame, strawberry flavour and magnesium stearate. None of the excipients are of animal or human origin and BSE/TSE risk-free declarations were provided for all of them.

Finished pharmaceutical product (FPP)

Pharmaceutical development and manufacture

The dispersible tablet is brick red, mottled, circular, uncoated and biconvex, having a deep score on one side and plain surface on the other side. The score line is only to facilitate breaking for ease of swallowing and not to divide into equal doses. The tablets are packed in Alu-Alu strips or in an LDPE bag put in a triple laminated sachet contained in an HDPE bottle with screw cap. The packing material was selected to protect the product from moisture and oxygen.

The pharmaceutical development was based on previous experience in this area and focussed on overcoming the inherent stability problems encountered with this type of 3-FDC dosage form. According to literature rifampicin is not only prone to hydrolysis and oxidation, but it can also react (indirectly through acid degradation or directly) with isoniazid to form a hydrazone. This hydrazone is described in the Ph.Int. monograph of rifampicin, isoniazid and pyrazinamide dispersible tablets. The selection of the excipients was based on their suitability to achieve the desired characteristics of the formulation and their compatibility with the APIs. As the dosage form is a dispersible tablet, sweeteners and flavouring agents play an important role in the formulation for patient acceptance. Aspartame and strawberry flavour were selected as the sweetener and flavouring agent, respectively.

The manufacture involves two separate wet granulation processes, one for isoniazid and the other for pyrazinamide. Rifampicin is introduced extra-granularly. Quick dispersion of the tablets are achieved through inclusion of intra- and extra-granular disintegrants. Appropriate in-process controls were set to ensure batch-to-batch reproducibility.

Specifications

The product specifications include tests for description, identification of the APIs (HPLC, TLC), average weight, hardness, friability, disintegration time (≤ 3 min.), fineness of dispersion, loss on drying, dissolution (HPLC detection), uniformity of dosage units (by content uniformity), related substances (HPLC), assay (HPLC), residual solvent and microbial limits. The test procedures have been adequately validated.

Stability testing

Stability studies have been conducted at 30°C/75%RH (zone IVb) as long-term storage condition and for 6 months at 40°C/75%RH as accelerated condition in both pack types proposed for marketing of the product. The data showed slight degradation of rifampicin, though the degradation products stayed well within agreed limits for both packaging configurations at these storage conditions. Based on the available stability data, the proposed shelf life and storage conditions as stated in the SmPC are acceptable. The in-use storage period (after first opening) as indicated in the product information for the HDPE bottle packs is supported by stability data.

Conclusion

The quality part of the dossier is accepted.

3. Assessment of Bioequivalence

The following bioequivalence study has been performed in 2017 according to internationally accepted guidelines.

Study title:

Four tablets as single oral dose fasting in vivo bioequivalence study of fixed dose combination of Rifampicin 75 mg, Isoniazid 50 mg and Pyrazinamide 150 mg dispersible tablets (Macleods Pharmaceuticals Limited, India) with separate formulation of one capsule of Rifadin® (rifampicin) capsules 300 mg (Sanofi-Aventis, USA), two tablets of Isoniazid tablets USP 100 mg (Sandoz Inc., USA) and one tablet of Pyrafat® (pyrazinamide) tablets 500 mg (Fatol Arzneimittel GmbH, Germany) in healthy adult, human subjects (study no. BEQ-2039-RIP(F)-2016).

The objective of the study was to compare the bioavailability of the stated Rifampicin/Isoniazid/Pyrazinamide 75mg/50mg/150mg FDC dispersible tablets manufactured for/by Macleods Pharmaceuticals Ltd., India (test drug) with the individual reference formulations Rifadin® (Sanofi-Aventis), Isoniazid USP (Sandoz Inc.) and Pyrafat® (Fatol Arzneimittel 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 treatments in a randomized fashion:

Treatment T:	Test – 4 tablets Rifampicin/Isoniazid/Pyrazinamide 75mg/50mg/150mg (rifampicin 300 mg + isoniazid 200 mg + pyrazinamide 600mg) Batch no. ERE7632B
Treatment R:	References – 1 capsule Rifadin® (rifampicin 300 mg) Batch no. 3130697

– 2 tablets Isoniazid USP
(isoniazid 200 mg)
Batch no. ME140742
– 1 tablet Pyrafat®
(pyrazinamide 500 mg)
Batch no. 014016

A 7 day wash-out period was observed between administration of test and reference. Serial blood samples (1 pre-dose sample and 19 samples within 72 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 rifampicin, isoniazid and pyrazinamide were analyzed using validated LC-MS/MS methods. The limit of quantification was stated to be about 100 ng/ml for rifampicin, 100 ng/ml for isoniazid and 500 ng/ml for pyrazinamde.

The study was performed with 24 participants; data generated from a total of 23 subjects were utilized for analysis to establish pharmacokinetic parameters and assess bioequivalence.

Arithmetic mean and geometric mean values of the pharmacokinetic variables for rifampicin, isoniazid and pyrazinamide as well as statistical results are summarised in the following tables:

Rifampicin

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)	1.41 ± 0.78	1.54 ± 0.76	-	-
C_{max} (ng/ml)	4949 ± 1182 (4826)	5497 ± 1181 (5410)	89.2	82.0 – 97.1
AUC_{0-t} (ng.h/ml)	27922 ± 7043 (27223)	30390 ± 6027 (29786)	91.4	86.1 – 97.0
AUC_{0-inf} (ng.h/ml)	29111 ± 7621 (--)	31644 ± 6370 (--)	--	--

* geometric mean

Isoniazid

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)	0.57 ± 0.45	0.81 ± 0.48	-	-
C_{max} (ng/ml)	4649 ± 1767 (4391)	4312 ± 1441 (4097)	107.2	94.3 – 121.8
AUC_{0-t} (ng.h/ml)	15835 ± 7564 (13892)	15964 ± 7982 (13739)	101.1	97.5 – 104.9
AUC_{0-inf} (ng.h/ml)	16544 ± 7846 (--)	16652 ± 8230 (--)	--	--

* geometric mean

Pyrazinamide

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)	0.69 ± 0.50	1.00 ± 0.64	-	-
C_{max} (ng/ml)	16740 ± 3746 (16377)	13492 ± 2588 (13277)	102.8	94.3 – 112.0
AUC_{0-t} (ng.h/ml)	181891 ± 33524 (179359)	154111 ± 26138 (151830)	98.4	95.3 – 101.7
AUC_{0-inf} (ng.h/ml)	194531 ± 32857 (--)	164324 ± 28109 (--)	--	--

* geometric mean; # dose normalised

The results of the study show that preset acceptance limits of 80 - 125 % are met by both AUC and C_{max} values regarding rifampicin, isoniazid and pyrazinamide. Accordingly, the test Rifampicin/Isoniazid/Pyrazinamide 75mg/50mg/150mg FDC dispersible tablets meets the criteria for bioequivalence with regard to the rate and extent of absorption and is therefore bioequivalent to the individual comparator products Rifadin® (Sanofi-Aventis), Isoniazid USP (Sandoz Inc.) and Pyrafat® (Fatol Arzneimittel GmbH).

4. Summary of Product Safety and Efficacy

Rifampicin/Isoniazid/Pyrazinamide 75mg/50mg/150mg Dispersible Tablets has been shown to conform to the same relevant standards of quality, efficacy and safety as those required of the comparator products. According to the submitted data on quality and bioavailability Rifampicin/Isoniazid/Pyrazinamide 75mg/50mg/150mg Dispersible Tablets is pharmaceutically and therapeutically equivalent and thus interchangeable with the comparator products {Rifadin® (Sanofi-Aventis), Isoniazid USP (Sandoz Inc.) and Pyrafat® (Fatol Arzneimittel GmbH)} for which benefits have been proven in terms of clinical efficacy.

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 be acceptable when Rifampicin/Isoniazid/Pyrazinamide 75mg/50mg/150mg Dispersible Tablets is used in accordance with the SmPC.

Bioequivalence

Rifampicin/Isoniazid/Pyrazinamide 75mg/50mg/150mg Dispersible Tablets has shown to be bioequivalent with Rifadin® (Sanofi-Aventis, USA), Isoniazid USP (Sandoz Inc., USA) and Pyrafat® (Fatol Arzneimittel GmbH, Germany).

Efficacy and Safety

Regarding clinical efficacy and safety, Rifampicin/Isoniazid/Pyrazinamide 75mg/50mg/150mg Dispersible Tablets is considered effective and safe when the guidance and restrictions in the summary of product characteristics (SmPC) are taken into consideration.

Benefit–risk Assessment

Based on the WHO assessment of data on quality, bioequivalence, safety and efficacy the team of assessors considered that the benefit–risk profile of Rifampicin/Isoniazid/Pyrazinamide 75mg/50mg/150mg Dispersible Tablets was acceptable for the following indication: **initial treatment of tuberculosis caused by drug-susceptible *Mycobacterium tuberculosis* in children,** and has advised that the quality, efficacy and safety of Rifampicin/Isoniazid/Pyrazinamide 75mg/50mg/150mg Dispersible Tablets allow inclusion of Rifampicin/Isoniazid/Pyrazinamide 75mg/50mg/150mg Dispersible Tablets, manufactured at Macleods Pharmaceuticals Limited, Phase II, Unit II, Premier Industrial Estate, Kachigam, Daman, 369 210 India, in the list of prequalified medicinal products.