

**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

<b>Name of the Finished Pharmaceutical Product:</b>	Isoniazid/Rifampicin 150 mg/150 mg Tablets*
<b>Manufacturer of Prequalified Product:</b>	Lupin Limited A-28/1, M.I.D.C Industrial area Chikalthana 431210 Aurangabad India TEL: +91-2402485871
<b>Active Pharmaceutical Ingredients (APIs):</b>	Isoniazid/Rifampicin
<b>Pharmaco-therapeutic group (ATC Code):</b>	Antimycobacterials, combinations of drugs for treatment of tuberculosis (J04AM02)
<b>Therapeutic indication:</b>	Isoniazid/Rifampicin 150 mg/150 mg Tablets is indicated for the continuation treatment phase of tuberculosis, caused by <i>Mycobacterium tuberculosis</i> in patients weighing more than 30kg.

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\* 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

Isoniazid/Rifampicin 150mg/150mg Tablets is indicated for the treatment of tuberculosis, caused by *Mycobacterium tuberculosis*. It is indicated for the continuation treatment phase of tuberculosis caused by *Mycobacterium tuberculosis* in patients weighing more than 30 kg .

Isoniazid/Rifampicin 150mg/150mg Tablets is not indicated for use in patients with clinically significant hypersensitivity to rifampicin, isoniazid or to any of the components contained in the formulation, and in patients with acute liver disease, icterus or severe liver impairment. Co-administration of Rifampicin/Isoniazid 150mg/150mg Tablets with voriconazole or any HIV or HCV protease inhibitor is contraindicated.

Isoniazid/Rifampicin 150mg/150mg 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 (APIs)

#### *Isoniazid*

Based on scientific principles the WHO Prequalification of Medicines Programme (PQP) has identified isoniazid (up to 300 mg oral dose) as a BCS class 3 API. Isoniazid is thus BCS highly soluble.

Isoniazid (reference number WHOAPI-086) 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 assurance that isoniazid, used in the manufacture of Isoniazid/Rifampicin 150mg/150mg Tablets, is of good quality and manufactured in accordance with WHO Good Manufacturing Practices. 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.

#### *Rifampicin*

Rifampicin is described in the Ph.Int., Ph.Eur. and the USP and is considered well-established in the WHO Prequalification Programme. The API, accepted through WHO's APIMF procedure, is in non-compacted form.

The API specifications, which are pharmacopoeial based, include tests for description, solubility, identification, crystallinity, pH, loss on drying, related substances (HPLC), assay, heavy metals, sulfated ash, residual solvents, tapped density, particle-size distribution and microbiological examination.

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.

### Other ingredients

Other ingredients used in the core tablet formulation include ascorbic acid, colloidal silicon dioxide, crospovidone, magnesium stearate, microcrystalline cellulose and pregelatinised starch. BSE/TSE-free certification has been provided for magnesium stearate.

The film coating contains hypromellose, iron oxide red, iron oxide yellow, polyethylene glycol, simethicone emulsion, talc and titanium dioxide.

## Finished Pharmaceutical Product (FPP)

### *Pharmaceutical development and manufacture*

The pharmaceutical product is a brown coloured, film-coated, circular, biconvex tablet, with break-line on one side and plain on the other side. The break-line is intended for subdivision of tablets when half a tablet dose is to be administered, as supported by divisibility studies. The tablets are packed in PVC/PVDC- aluminium blister cards and in a polypropylene bag, inside an HDPE container with aluminium tagger seal, also containing a silica gel bag and closed with a white LDPE cap.

The development of the final composition of the tablets has been described. The selection of the excipients was based on prior knowledge of TB fixed-dose combination tablets. Ascorbic acid has been included to protect rifampicin from oxidation. According to literature, rifampicin and isoniazid may react to form a hydrazone, 3-(isonicotinoylhydrazinomethyl) rifamycin. In the selected process the APIs are partially protected from interaction by means of separate granulation steps. Moisture pick-up studies showed that the product should be protected from high humidity.

Appropriate in-process controls were set to ensure batch-to-batch reproducibility. Validation data presented demonstrated the consistency of the process and the quality of the product.

### *Specifications*

The product specifications include tests for description, identification of the APIs (HPLC and TLC) and colorants, average and uniformity of weight, tablet dimensions, dissolution, assay (HPLC) and related substances (HPLC).

### *Stability testing*

Stability studies have been performed at 30°C/65%RH as long-term conditions and for six months at accelerated conditions in both packaging configurations intended for marketing of the product. The data showed a decrease in rifampicin assay value with a concomitant slight increase in rifampicin-related degradation products, though remaining within agreed limits. An in-use period of 30 days after first opening has been demonstrated for the bulk bottle pack. Based on the available stability data, the proposed shelf life and storage conditions 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 2011 according to internationally accepted guidelines.

A randomized, open label, balanced, single center, two treatment, two period, two sequence, single dose, crossover oral bioequivalence study of two tablets of fixed dose combination of Isoniazid/Rifampin 150 mg/ 150 mg tablets manufactured by Lupin Limited, India and one capsule of Rimactan (rifampin) capsule 300 mg manufactured by Sandoz Farmaceutica S.A., Spain and three tablets of Isozid<sup>®</sup> 100 mg (isoniazid) tablets manufactured by Riemser Arzneimittel AG, Germany, in healthy human adult male subjects, under fasting conditions. (study no. S-11-303).

The objective of the study was to compare the rate and extent of absorption of the stated fixed dose combination tablet Isoniazid/Rifampicin 150mg/150 mg with the same dose of the individual references Rimactan<sup>®</sup> 300 mg capsules and Isozid<sup>®</sup> 100 mg tablets. The comparison was performed as a randomized, two-treatment, two-period, single-dose, crossover study in healthy male subjects under fasting conditions. Subjects were assigned to receive the following two treatments:

- Treatment T: Test – 2 x Isoniazid/Rifampicin 150mg/150 mg tablets  
(isoniazid 300 mg + rifampicin 300 mg)  
Batch no. GB11001
- Treatment R: Reference – 1 x Rimactan<sup>®</sup> 300 capsule  
(rifampicin 300 mg )  
Batch no. KW10J322  
Reference – 3 x Isozid<sup>®</sup> 100 tablet  
(isoniazid 300 mg )  
Batch no. 001031

A 5 day wash-out period was observed between administration of test and reference. Serial blood samples (1 pre-dose sample and 16 samples within 48 h post dose) were taken during each study period to obtain bioavailability characteristics  $AUC_{inf}$ ,  $AUC_{0-t}$ ,  $C_{max}$  and  $t_{max}$  for bioequivalence evaluation. Drug concentrations for rifampicin and isoniazid in plasma were analyzed using a validated LC/MS/MS method. The limit of quantification was stated to be 65 ng/ml for rifampicin and 400 ng/ml for isoniazid.

The study was performed with 36 participants, data generated from a total of 27 subjects were utilized for analysis to establish pharmacokinetic parameters and assess bioequivalence.

Arithmetic means ( $\pm$  sd), geometric means ( $AUC$ ,  $C_{max}$ ) for rifampicin and isoniazid as well as statistical results are summarised in the following tables:

### Rifampicin

Pharmacokinetic Parameter	Test formulation (T) arithm.mean ( $\pm$ SD)	Reference (R) arithm. mean ( $\pm$ SD)	log-transformed parameters	
			Ratio T/R (%)	Conventional 90% CI (ANOVAlog)
$t_{max}$ (h)	1.89 $\pm$ 0.73	1.94 $\pm$ 0.77	-	-
$C_{max}$ (ng/ml)	4271 $\pm$ 1017 (4157)*	4627 $\pm$ 1138 (4491)*	92.6	87.4 – 98.1
$AUC_{0-t}$ (ng.h/ml)	23761 $\pm$ 5427 (23203)*	25364 $\pm$ 6619 (24506)*	94.6	90.1 – 99.5
$AUC_{0-inf}$ (ng.h/ml)	26068 $\pm$ 6318 (25404)*	28194 $\pm$ 6751 (27399)*	92.7	88.7 – 97.0

\* geom. mean

**Isoniazid**

Pharmacokinetic Parameter	Test formulation (T) arithm.mean ( $\pm$ SD)	Reference (R) arithm. mean ( $\pm$ SD)	log-transformed parameters	
			Ratio T/R (%)	Conventional 90% CI (ANOVAlog)
$t_{\max}$ (h)	0.69 $\pm$ 0.27	1.02 $\pm$ 0.50	-	-
$C_{\max}$ ( $\mu$ g/ml)	7.90 $\pm$ 2.34 (7.57)*	6.86 $\pm$ 1.96 (6.62)*	114.3	104.6 – 124.7
AUC <sub>0-t</sub> ( $\mu$ g.h/ml)	25.3 $\pm$ 12.2 (23.0)*	26.0 $\pm$ 12.2 (23.6)*	97.4	91.2 – 104.0
AUC <sub>0-inf</sub> ( $\mu$ g.h/ml)	28.1 $\pm$ 14.0 (25.5)*	29.6 $\pm$ 14.2 (26.8)*	95.3	88.8 – 102.4

\* geom. mean

The results of the study show that preset acceptance limits of 80 -125 % are met by both AUC and  $C_{\max}$  values regarding rifampicin and isoniazid. Accordingly, the test fixed dose combination tablet Isoniazid/Rifampicin 150mg/150 mg tablets (Lupin Ltd., India), meets the criteria for bioequivalence with regard to rate and extent of absorption and is therefore bioequivalent to the individual reference compounds, Rimactan<sup>®</sup> 300 mg capsule (Sandoz Farmaceutica) and Isozid<sup>®</sup> 100 mg tablet (Riemser Arzneimittel AG).

**4. Summary of Product Safety and Efficacy**

Isoniazid/Rifampicin 150mg/150mg Tablets has been shown to conform to the same relevant standards of quality, efficacy and safety as those required of the innovator products. According to the submitted data on quality and bioavailability Isoniazid/Rifampicin 150mg/150mg Tablets is pharmaceutically and therapeutically equivalent and thus interchangeable with the reference products Rimactan<sup>®</sup> 300 mg Capsules (Rifampicin 300mg Capsules) and Isozid<sup>®</sup> 100 mg Tablets ( Isoniazid 100mg Tablets).

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 Isoniazid/Rifampicin 150mg/150mg Tablets is used in accordance with the SmPC.

**Bioequivalence**

Isoniazid/Rifampicin 150mg/150mg Tablets has shown to be bioequivalent with Rimactan<sup>®</sup> (Sandoz Farmaceutica S.A., Spain,) and Isozid (Riemser Arzneimittel AG, Germany)

**Efficacy and Safety**

Regarding clinical efficacy and safety, Isoniazid/Rifampicin 150mg/150mg Tablets is considered effective and safe to use when the guidance and restrictions in the Summary of Product Characteristics 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 Isoniazid/Rifampicin 150mg/150mg Tablets was acceptable for the following indication: "the continuation treatment phase of tuberculosis, caused by *Mycobacterium tuberculosis* in patients weighing more than 30 kg", and has advised that the quality, efficacy and safety of Isoniazid/Rifampicin 150mg/150mg Tablets allow inclusion of Isoniazid/Rifampicin 150mg/150mg Tablets, manufactured at Lupin Limited, A-28/1, M.I.D.C Industrial area, Chikalhana, 431210 , Aurangabad, India, in the list of prequalified medicinal products.