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:	Isoniazid/Pyridoxine hydrochloride/ Sulfamethoxazole/Trimethoprim 300 mg/25 mg/800 mg/160 mg Tablets[1]
Manufacturer of Prequalified Product:	Cipla Limited Unit I, Plot No. A-2, A-33, MIDC, Patalganga District - Raigad, Maharashtra Pin code: 410 220, India
Active Pharmaceutical Ingredient (API):	Isoniazid Pyridoxine hydrochloride Sulfamethoxazole Trimethoprim
Pharmaco-therapeutic group (ATC Code):	Isoniazid: antimycobacterial (J04AC01) Pyridoxine: other plain vitamin preparations (A11HA02) Sulfamethoxazole/trimethoprim: combinations of sulphonamides and trimethoprim, including derivatives (J01EE01)
Therapeutic indication:	Isoniazid/Pyridoxine hydrochloride/ Sulfamethoxazole/Trimethoprim 300 mg/25 mg/800 mg/160 mg Tablets is indicated for HIV-infected adults, adolescents and children for the prevention of opportunistic infections particularly tuberculosis, *Pneumocystis jiroveci* (*P. carinii*) pneumonia, *Plasmodium falciparum* malaria, toxoplasmosis and bacterial infections sensitive to sulfamethoxazole/trimethoprim.

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

Isoniazid/Pyridoxine hydrochloride/Sulfamethoxazole/Trimethoprim 300 mg/25 mg/800 mg/160 mg Tablets is indicated for HIV-infected adults, adolescents and children for the prevention of opportunistic infections particularly tuberculosis, *Pneumocystis jiroveci* (*P. carinii*) pneumonia, *Plasmodium falciparum* malaria, toxoplasmosis and bacterial infections sensitive to sulfamethoxazole/trimethoprim.

Isoniazid/Pyridoxine hydrochloride/Sulfamethoxazole/Trimethoprim 300 mg/25 mg/800 mg/160 mg Tablets should be used in accordance with official guidelines on the prevention of opportunistic infections in individuals with HIV infection, taking into account local prevalence of tuberculosis, malaria and relevant bacterial infections.

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)

CEPs (Certificates of Suitability) issued by the EDQM were submitted for sulfamethoxazole, trimethoprim and pyridoxine hydrochloride, ensuring good manufacturing control and applicability of the respective Ph.Eur monographs to control the quality of the APIs. Additional user requirements for the two BCS low-solubility APIs (sulfamethoxazole and trimethoprim) include particle size distribution, the limits of which were set on the data obtained for the API batches used in the manufacture of the FPP biobatch.

Isoniazid 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 Isoniazid/Pyridoxine hydrochloride/Sulfamethoxazole/ Trimethoprim 300 mg/25 mg/800 mg/160 mg 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 inspection of the sites of API manufacture to verify compliance with WHO GMP requirements.

Other ingredients

Other ingredients used in the tablet formulation include maize starch, sodium starch glycolate, povidone, docusate sodium benzoate and magnesium stearate. None of the excipients are of animal or human origin.

Finished pharmaceutical product (FPP)

Pharmaceutical development and manufacture

The fixed-dose combination product is a white to off-white capsule-shaped, biconvex uncoated tablet scored on both sides. The score line is intended for division of tablets when half a tablet dose is to be administered. The tablets are packaged in HDPE bottles.

The development of the multisource product has been described. The selection of the excipients was primarily based on the qualitative composition of one of the comparator products, Septrin® 160 mg/800 mg Forte Tablets (containing 160 mg trimethoprim and 800 mg sulfamethoxazole per tablet) and API-excipient compatibility studies. Subsequent assurance of compatibility was provided by the long-term and accelerated stability studies. API-API studies showed that the APIs are compatible. Initially, the quality target product profile (QTPP) was defined based on the properties of

the APIs, characterization of the individual comparator products, consideration of the individual comparator product labels and intended patient population.

The wet granulation process was selected as a process of choice, since the average weight of tablet is high and the tablet mainly comprises of actives. During optimization studies the dissolution profiles of the comparator products were targeted. Satisfactory in-process controls have been established.

Specifications

The finished product specifications include tests for description, identification (HPLC and TLC), average weight and weight variation, friability, hardness, disintegration time, water content, uniformity of dosage units (by mass variation for sulfamethoxazole and content variation for the other 3 APIs), dissolution (HPLC detection), assay (HPLC), related substances (HPLC) and microbiological examination of non-sterile products. The analytical methods have been adequately validated.

Stability testing

Stability studies have been conducted 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 proved to be quite stable at these storage conditions, with little degradation observed. Data submitted showed that light protection is not needed. 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 2014 according to internationally accepted guidelines.

A study to evaluate the relative bioavailability of sulfamethoxazole, trimethoprim and isoniazid between a Test formulation of Isoniazid/Pyridoxine hydrochloride/Sulfamethoxazole/Trimethoprim 300 mg/25 mg/800 mg/160 mg Tablets (Cipla Ltd, India) and Septrin® Forte (sulfamethoxazole/trimethoprim) tablets, 800 mg/160 mg (manufactured by Glaxo Wellcome GmbH & Co. KG) co-administered with Isoniazid tablet, 300 mg (Sandoz Inc. USA) in healthy adult subjects under fasting conditions (study no. 11357201).

The objective of the study was to compare the bioavailability of the stated Isoniazid/Pyridoxine hydrochloride/Sulfamethoxazole/Trimethoprim 300 mg/25 mg/800 mg/160 mg Tablets manufactured by/for Cipla Ltd, India (test drug) with the reference formulations Septrin® Forte (Glaxo Wellcome GmbH & Co. KG) and Isoniazid 300 mg tablet (Sandoz Inc.) and to assess bioequivalence. The comparison was performed as a single-centre, open-label, randomised, crossover study in healthy subjects under fasting conditions. Each subject was assigned to receive each of the following two treatments in a randomised fashion:

Treatment T:	Test – 1 tablet Isoniazid/Pyridoxine hydrochloride/Sulfamethoxazole/Trimethoprim 300 mg/25 mg/800 mg/160 mg (isoniazid 300 mg + pyridoxine hydrochloride 25 mg + sulfamethoxazole 800 mg + trimethoprim 160 mg) Batch no. KXX3014.
Treatment R:	References – 1 tablet Septrin® Forte (sulfamethoxazole 800 mg + trimethoprim 160 mg) Batch no. B0050D. 1 tablet Isoniazid 300 mg (isoniazid 300 mg) Batch no. ME120939

A 7-day wash-out period was observed between administration of test and reference. Serial blood samples (1 pre-dose sample and 26 samples within 72 hours after dosing) were taken during each study period to obtain bioavailability characteristics AUC, C_{max} and t_{max} for bioequivalence evaluation. Drug concentrations for sulfamethoxazole, trimethoprim and isoniazid were analysed using validated LC-MS/MS methods. The limit of quantification was stated to be about 0.50 µg/ml for sulfamethoxazole, 10 ng/ml for trimethoprim and 20 ng/ml for isoniazid.

The study was performed with 28 participants; data generated from a total of 28 subjects were used for analysis to establish pharmacokinetic parameters and assess bioequivalence.

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

Sulfamethoxazole

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} (hour)	2.54 ± 0.86	3.18 ± 0.71	-	-
C_{max} (µg/ml)	54.1 ± 11.1 (52.9)	52.3 ± 10.6 (51.3)	103.2	99.5–107.0
AUC_{0-t} (µg·hour/ml)	791 ± 147 (778)	798 ± 176 (779)	99.8	96.2–103.5
AUC_{0-inf} (µg·hour/ml)	816 ± 151 (802)	816 ± 174 (798)	100.5	97.0–104.1

* geometric mean

Trimethoprim

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} (hour)	2.10 ± 1.00	1.96 ± 0.86	-	-
C_{max} (ng/ml)	1679 ± 470 (1616)	1704 ± 464 (1645)	98.2	93.4–103.3
AUC_{0-t} (ng·hour/ml)	26675 ± 7988 (25504)	27399 ± 8114 (26240)	97.2	93.7–100.9
AUC_{0-inf} (ng·hour/ml)	27112 ± 8106 (25927)	27822 ± 8145 (26669)	97.2	93.7–100.9

* 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} (hour)	0.84 ± 0.50	0.79 ± 0.38	-	-
C_{max} (ng/ml)	6234 ± 2218 (5833)	6074 ± 2256 (5593)	104.3	95.1–114.4
AUC_{0-t} (ng·hour/ml)	26657 ± 17891 (20995)	26556 ± 18630 (20230)	103.8	99.5–108.3
AUC_{0-inf} (ng·hour/ml)	27128 ± 18298 (21307)	27040 ± 19069 (20542)	103.7	99.5–108.2

* 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 sulfamethoxazole, trimethoprim and isoniazid. For pyridoxine very rapid or rapid dissolution was shown at pH 1.2, 4.5 and 6.8. Accordingly, the test FDC tablet Isoniazid/Pyridoxine hydrochloride/Sulfamethoxazole/Trimethoprim 300 mg/25 mg/800 mg/160 mg meets the criteria for bioequivalence with regard to the rate and extent of absorption and is therefore bioequivalent to the reference Septrin® Forte (Glaxo Wellcome GmbH & Co. KG) and Isoniazid 300 mg tablet (Sandoz Inc.).

4. Summary of Product Safety and Efficacy

Isoniazid/Pyridoxine hydrochloride/Sulfamethoxazole/Trimethoprim 300 mg/25 mg/800 mg/160 mg Tablets 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 Isoniazid/Pyridoxine hydrochloride/Sulfamethoxazole/Trimethoprim 300 mg/25 mg/800 mg/160 mg Tablets is pharmaceutically and therapeutically equivalent and thus interchangeable with the reference Septrin® Forte (Glaxo Wellcome GmbH & Co. KG) and Isoniazid 300 mg tablet (Sandoz Inc.) for which benefits have been proven in terms of clinical efficacy.

The clinical safety of this product is considered 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/Pyridoxine hydrochloride/ Sulfamethoxazole/Trimethoprim 300 mg/25 mg/800 mg/160 mg Tablets is used in accordance with the SmPC.

Bioequivalence

Isoniazid/Pyridoxine hydrochloride/Sulfamethoxazole/Trimethoprim 300 mg/25 mg/800 mg/160 mg Tablets has shown to be bioequivalent with Septrin® Forte (Glaxo Wellcome GmbH & Co. KG) and Isoniazid 300 mg tablet (Sandoz Inc.)

Efficacy and Safety

Regarding clinical efficacy and safety, Isoniazid/Pyridoxine hydrochloride/Sulfamethoxazole/ Trimethoprim 300 mg/25 mg/800 mg/160 mg 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 WHO's assessment of data on quality, bioequivalence, safety and efficacy the team of assessors considered that the benefit–risk profile of Isoniazid/Pyridoxine hydrochloride/ Sulfamethoxazole/Trimethoprim 300 mg/25 mg/800 mg/160 mg Tablets was acceptable for the following indication: "for HIV-infected adults, adolescents and children weighing over 14 kg for the prevention of opportunistic infections particularly tuberculosis, *Pneumocystis jiroveci* (*P. carinii*) pneumonia, *Plasmodium falciparum* malaria, toxoplasmosis and bacterial infections sensitive to sulfamethoxazole/trimethoprim" and has advised that the quality, efficacy and safety of Isoniazid/ Pyridoxine hydrochloride/Sulfamethoxazole/Trimethoprim 300 mg/25 mg/800 mg/160 mg Tablets allow inclusion of Isoniazid/Pyridoxine hydrochloride/Sulfamethoxazole/Trimethoprim 300 mg/25 mg/800 mg/160 mg Tablets, manufactured at Cipla Limited, Patalganga, India in the list of prequalified medicinal products.