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	[HA762 trade name]*
Manufacturer of Prequalified Product	Mylan Laboratories Limited Plot No. 11,12 & 13 Special Economic Zone, Pharma Zone Phase-II, Sector-III, Pithampur-454775 Dist. Dhar, Madhya Pradesh India
Active Pharmaceutical Ingredient(s) (API)	Isoniazid/Pyridoxine hydrochloride/ Sulfamethoxazole/Trimethoprim
Pharmaco-therapeutic group (ATC Code)	Isoniazid (Pharmacotherapeutic group: antimycobacterial) ATC code: J04AC01 Pyridoxine (Pharmacotherapeutic group: other plain vitamin preparations) ATC code: A11HA02 Sulfamethoxazole/trimethoprim (Pharmacotherapeutic group: combinations of sulphonamides and trimethoprim, including derivatives) ATC code: J01EE01
Therapeutic indication	[HA762 trade name] is indicated for preventing certain opportunistic infections in people living with HIV. It is for use in adults, adolescents and children weighing over 14 kg to prevent tuberculosis, *Pneumocystis jiroveci* (*P. carinii*) pneumonitis, *Plasmodium falciparum* malaria, toxoplasmosis and bacterial infections sensitive to sulfamethoxazole/trimethoprim.

1. Introduction

[HA762 trade name] is indicated in the prevention of certain opportunistic infections in individuals living with HIV, as detailed in the summary of product characteristics.

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*.

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

Active pharmaceutical Ingredient (API)

Isoniazid

Based on scientific principles the WHO Prequalification Team – Medicines (PQTm) has identified isoniazid (up to 300mg oral dose) as a BCS class 3 API. The API is thus BCS highly soluble.

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 [HA762 trade name], 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.

Pyridoxine, sulfamethoxazole and trimethoprim

CEPs (Certificates of Suitability) issued by the EDQM were submitted for pyridoxine, sulfamethoxazole and trimethoprim ensuring good manufacturing control and applicability of the respective Ph.Eur monographs to control the quality of the APIs. Additional user requirements for the BCS low soluble sulfamethoxazole 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.

Other ingredients

Other ingredients used in the core tablet formulation include microcrystalline cellulose, hydroxypropyl cellulose, sodium starch glycolate, colloidal silicon dioxide, stearic acid, partially pregelatinized maize starch, docusate sodium, low-substituted hydroxypropyl cellulose and magnesium stearate, all being pharmacopeial controlled. The commercially sourced proprietary film-coating mixture contains hypromellose, titanium dioxide, macrogol/PEG, talc, iron oxide yellow and iron oxide red. TSE/BSE free certificates have been provided for all the excipients.

Finished pharmaceutical product (FPP)

Pharmaceutical development and manufacture

The multisource product is a brown, film-coated, oval shaped, biconvex, bevel edge, scored tablet debossed with "S and T on either side of score line" on one side and "I and M on either side of score line" on the other side. The score line is intended for subdivision of tablets when half a tablet dose is to be administered. The tablets are packaged in HDPE bottles and cold form Alu/OPA/PVC/Alu blisters.

The objective of the development of the multisource product was to formulate a pharmaceutically acceptable, stable product bioequivalent to the WHO recommended comparator products, Bactrim™ DS (sulphamethoxazole/ trimethoprim 800mg/160mg) tablets, Isozid® (isoniazid 100mg) tablets and pyridoxine tablets (Versa Pharma Incorporated). The selection of the excipients was primarily based on API-API and API-excipient compatibility studies, characterisation of the comparator products and prior experience of manufacturing similar types of solid oral immediate release tablet dosage forms. The manufacturing process involving dry granulation was selected considering the moisture sensitivity of isoniazid and low dose of pyridoxine hydrochloride; also considering the poor flow property of both sulfamethoxazole and trimethoprim APIs, wet granulation was selected to improve the uniform distribution of the APIs in the FPP. Various experiments were performed to select and optimize the concentration of excipients and other process parameters to obtain tablets of desired characteristics. 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 finished product specifications include tests for description, identification of the APIs (HPLC and HPLC with PDA detection) and colourants, uniformity of dosage units (by content uniformity), dissolution (HPLC detection), assay (HPLC), related substances (HPLC), water content (KF), uniformity of mass (for subdivided tablets) 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 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 2020 according to internationally accepted guidelines:

A randomized, balanced, two-treatment, two-period, two-sequence, single-dose, crossover oral bioequivalence study of isoniazid, pyridoxine, sulphamethoxazole and trimethoprim tablets (300mg/25mg/800mg/160 mg) of Mylan Laboratories Limited, India with Reference product (R = R1: Isozid® 100 mg tabletten (isoniazid tablets) Riemser Pharma GmbH An der Wiak 7-17493 Grelfswald-Insel Riems + R2: Bactrim™ DS (sulphamethoxazole and trimethoprim 800mg/160mg) tablets Sun pharmaceutical Inc USA in normal healthy adult human subjects under fasting conditions (study no. C18258).

The objective of the study was to compare the bioavailability of the stated Isoniazid/Pyridoxine/Sulfamethoxazole/Trimethoprim 300mg/25mg/800mg/160mg FDC tablet manufactured for/by Mylan Laboratories Ltd., India (test drug) with the reference formulations Isozid® 100 mg tablet (Riemser Pharma GmbH) and Bactrim® DS 800/160 mg tablet (Sun Pharmaceuticals Inc.) and to assess bioequivalence. The comparison was performed as a single centre, open label, single dose, 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 – 1 tablet Isoniazid/Pyridoxine/Sulfamethoxazole/Trimethoprim 300mg/25mg/800mg/160 mg
(isoniazid 300 mg + pyridoxine 25 mg + sulphamethoxazole 800 mg + trimethoprim 160 mg)
Batch no.: 2017998

Treatment R: References
– 3 tablets Isozid® 100 mg
(isoniazid 300 mg)
Batch no. 002017
– 1 tablets Bactrim® DS 800/160 mg

(sulphamethoxazole 800 mg + trimethoprim 160 mg)
Batch no. 6851001

An 8-day wash-out period was observed between administration of test and references. Serial blood samples (1 pre-dose sample and 24 samples within 48 hours post dose) were taken during each study period to obtain bioavailability characteristics AUC, C_{max} and t_{max} for bioequivalence evaluation. Drug concentrations for isoniazid, sulphamethoxazole and trimethoprim were analyzed using validated LC-MS/MS methods. The limit of quantification was stated to be about 50 ng/mL for isoniazid, about 1002 ng/mL for sulphamethoxazole and about 30 ng/mL trimethoprim.

The study was performed with 40 participants. Data generated from a total of 38 subjects were utilized for analysis to establish pharmacokinetic parameters and assess bioequivalence.

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

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)#	0.67 (0.33 – 2.33)	0.50 (0.33 – 2.67)	-	-
C_{max} (ng/mL)	9466 ± 3231 (8945)	8783 ± 2178 (8513)	105.1	95.6 – 115.4
AUC_{0-t} (ng.h/mL)	33155 ± 14457 (29149)	32751 ± 14033 (29105)	100.2	97.5 – 102.9
AUC_{0-inf} (ng.h/mL)	33846 ± 14751 (29763)	33351 ± 14306 (29632)	100.4	97.8 – 103.2

*geometric mean; # median (range)

Sulphamethoxazole

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)#	2.00 (0.67 – 4.50)	2.00 (0.50 – 5.00)	-	-
C_{max} (µg/mL)	55.8 ± 6.5 (55.5)	51.7 ± 7.0 (51.2)	108.3	105.2 – 111.4
AUC_{0-t} (µg.h/mL)	722 ± 105 (714)	707 ± 106 (699)	102.2	99.6 – 104.8
AUC_{0-inf} (µg.h/mL)	758 ± 110 (749)	737 ± 103 (729)	102.7	100.6 – 104.9

*geometric mean; # median (range)

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} (h)#	2.00 (0.50 – 4.50)	0.75 (0.33 – 3.52)	-	-
C_{max} (ng/mL)	1434 ± 259 (1411)	1617 ± 332 (1584)	89.1	84.2 – 94.3
AUC_{0-t} (ng.h/mL)	19901 ± 3898 (19524)	20045 ± 3965 (19659)	99.3	96.1 – 102.7
AUC_{0-inf} (ng.h/mL)	21059 ± 4248 (20636)	21174 ± 4187 (20768)	99.4	96.3 – 102.5

*geometric mean; # median (range)

The results of the study show that preset acceptance limits of 80 -125 % are met by both AUC and C_{max} values regarding isoniazid, sulphamethoxazole and trimethoprim.
As per WHO guidance, for pyridoxine very rapid dissolution was shown at pH 1.2, 4.5 and 6.8.

Accordingly, the test Isoniazid/Pyridoxine/Sulphamethoxazole/Trimethoprim 300/25/800/160 mg FDC tablet meets the criteria for bioequivalence with regard to the rate and extent of absorption and is therefore bioequivalent to the references Isozid® 100 mg (Riemser Pharma GmbH) and Bactrim™ DS 800/160 mg tablet (Sun Pharmaceuticals Inc.).

4. Summary of product safety and efficacy

[HA762 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, [HA762 trade name] is pharmaceutically and therapeutically equivalent and thus interchangeable with the comparator products formulations Isozid® 100 mg tablet (Riemser Pharma GmbH) and Bactrim® DS 800/160 mg tablet (Sun Pharmaceuticals Inc.), for which benefits have been proven in terms of clinical efficacy. The clinical safety of [HA762 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 [HA762 trade name] is used in accordance with the SmPC.

Bioequivalence

[HA762 trade name] has been shown to be bioequivalent with the formulations Isozid® 100 mg tablet (Riemser Pharma GmbH) and Bactrim® DS 800/160 mg tablet (Sun Pharmaceuticals Inc.).

Efficacy and Safety

Regarding clinical efficacy and safety, [HA762 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 [HA762 trade name] was acceptable for the following indication: 'for preventing certain opportunistic infections in people living with HIV. It is for use in adults, adolescents and children weighing over 14 kg to prevent tuberculosis, *Pneumocystis jiroveci* (*P. carinii*) pneumonitis, *Plasmodium falciparum* malaria, toxoplasmosis and bacterial infections sensitive to sulfamethoxazole/trimethoprim', and would allow inclusion of [HA762 trade name], manufactured at Mylan Laboratories Limited, Plot No. 11, 12 & 13, Special Economic Zone, Pharma Zone Phase-II, Sector-III, Pithampur-454775, Dist. Dhar, Madhya Pradesh, India, in the list of prequalified medicinal products.