SCIENTIFIC DISCUSSION

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.

Name of the Finished Pharmaceutical Product:	[HA691 trade name] *
Manufacturer of Prequalified Product:	Milan Laboratories (India) Pvt Ltd Plot No. 35/36/63/64/65/67 Jawahar Coop Industrial Estate Ltd Kamothe, Panvel Navi Mumbai Maharashtra 410 209 India
Active Pharmaceutical Ingredient (API):	Sulfamethoxazole/Trimethoprim
Pharmaco-therapeutic group (ATC Codes):	Antibacterials for systemic use, combinations of sulfonamides and trimethoprim: sulfamethoxazole and trimethoprim (J01EE01)
Therapeutic indication:	[HA691 trade name] is indicated for the treatment and prevention of infections susceptible to sulfamethoxazole/trimethoprim in patients with HIV infection. Such infections include *Pneumocystis jiroveci* pneumonitis, toxoplasmosis encephalitis, *Plasmodium falciparum* malaria, norcardiosis, brucellosis and certain bacterial infections.

1. Introduction

[HA691 trade name] is indicated for the treatment and prevention of infections susceptible to sulfamethoxazole/trimethoprim in patients with HIV infection. Such infections include *Pneumocystis jiroveci* pneumonitis, toxoplasmosis encephalitis, *Plasmodium falciparum* malaria, norcardiosis, brucellosis and certain bacterial infections.

[HA691 trade name] should be initiated by a health care provider experienced in the management of HIV 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)

Sulfamethoxazole

A CEP (Certificate of Suitability) issued by the EDQM was submitted for sulfamethoxazole ensuring good manufacturing control and applicability of the Ph.Eur monograph to control the quality of the API. Additional user requirements for the BCS low soluble sulfamethoxazole include particle size

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

distribution, the limits of which were set on the data obtained for the API batch used in the manufacture of the FPP biobatch.

Trimethoprim

Trimethoprim, 5-(3,4,5-trimethoxybenzyl) pyrimidine-2,4-diamine, is manufactured in several steps from dimethyl amine, acrylonitrile and guanidine nitrate. The specifications and test methods for the isolated intermediates are considered to be satisfactory. The structure of trimethoprim was confirmed by the route of synthesis and spectrometric data. Trimethoprim is known to exhibit polymorphism and exists in four forms, namely Form I, II, III and IV and hydrate forms. Form I which is the most stable polymorphic form is consistently produced.

The API specifications are pharmacopoeial based and include tests for appearance, solubility, identification (IR or UV, melting point and a chemical test), appearance of solution, related substances (HPLC and GC) loss on drying, sulphated ash, assay (potentiometry), residual solvents (GC), nitrobenzene content (HPLC), benzene and acrylonitrile content (GC), polymorphic identity (XRPD), bulk/tapped density 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.

Other ingredients

Other ingredients used in the tablet formulation include povidone, magnesium stearate, docusate sodium and sodium starch glycolate. All the excipients are conventional pharmaceutical ingredients included in the formulation at suitable levels and for recognised purposes. None of the excipients are of animal or human origin. TSE/BSE free certificates have been provided for all the excipients.

Finished pharmaceutical product (FPP)

Pharmaceutical development and manufacture

The multisource product is a white-coloured, capsule-shaped tablet, debossed with ‘M’ and ‘L’, separated by a score-line on one side and plain on the other side. The tablets are packaged in PVC-Aluminium blisters and in either white ribbed HDPE containers with transparent polyethene bags and aluminium tagger seal and closed with white round HDPE caps or white opaque round HDPE containers and closed with white opaque polypropylene caps with induction wad sealing.

The objective of the development of the multisource product was to formulate a stable product bioequivalent to the WHO recommended comparator product, Septrin Forte® tablets 800mg/160mg. The selection of the excipients was primarily based on the excipients used in the comparator product. API-API and API-API-excipient compatibility studies did not reveal any incompatibilities. Direct compression of the blend was not considered due to poor powder flow and high content of the APIs in the finished product, thus aqueous wet granulation was selected as the manufacturing process. Based on the satisfactory data of optimization trials, the formulation was finalized resulting in a product matching the quality target product profile. Appropriate in-process controls were set to ensure batch-to-batch reproducibility.

Specifications

The finished product specifications are pharmacopoeia based and include tests for description; identification (IR and TLC); weight of 20 tablets; average weight; uniformity of weight; hardness; tablet dimensions; disintegration time; friability; uniformity of dosage units (by content uniformity); water content; assay (potentiometry, UV and HPLC); dissolution (HPLC detection); related substances (HPLC); 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. Based on the available stability data, the proposed shelf life and storage conditions as stated in the SmPC are acceptable. The tablets must be protected from light.

Conclusion

The quality part of the dossier is accepted.

3. Assessment of Bio-Equivalence

The following bioequivalence study has been performed in 2016 according to internationally accepted guidelines.

An open label, balanced, randomized, two treatment, two period, two sequence, single oral dose, crossover, bioequivalence study of Betrim Forte {Cotrimoxazole tablet BP 960 mg (Sulfamethoxazole BP 800 mg and Trimethoprim BP 160 mg)} of Milan Laboratories (India) Pvt. Ltd., with Septrin Forte tablet (Sulfamethoxazole BP 800 mg and Trimethoprim BP 160 mg) of Aspen Pharma Trading Limited, 3016 Lake Drive, Citywest Business Campus, Dublin 24, Ireland in normal, healthy, adult, human subjects under fasting condition (Study no. PCLPL-147-15).

The objective of the study was to compare the bioavailability of the stated Sulfamethoxazole/ Trimethoprim 800mg/160mg FDC tablet manufactured by/for Milan Labs Pvt., India (test drug) with the reference formulation Septrin Forte® (Aspen Pharma Trading Limited) 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 two treatments in a randomized fashion:

Treatment T:	Test – 1 tablet Sulfamethoxazole /Trimethoprim 800mg/160 mg (Sulfamethoxazole 800 mg + Trimethoprim 160 mg) Batch no. MG16085
Treatment R:	Reference – 1 tablet Septrin Forte® (Sulfamethoxazole 800 mg + Trimethoprim 160 mg) Batch no. B00415E

An 11-day wash-out period was observed between administration of test and reference. Serial blood samples (1 pre-dose sample and 22 samples within 72 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 sulfamethoxazole and trimethoprim were analyzed using a validated LC-MS/MS method. The limit of quantification was stated to be about 1020 ng/mL for sulfamethoxazole and 31 ng/mL for trimethoprim.

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 sulfamethoxazole and trimethoprim as well as statistical results are summarized 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} (h)[#]	3.23 ± 0.89	3.87 ± 4.53	-	-

C_{max} (µg/mL)	48.0 ± 7.3 (47.5)	52.4 ± 9.2 (51.8)	91.7	87.8 – 95.8
AUC_{0-72h} (µg.h/mL)	714 ± 89 (710)	782 ± 232 (763)	93.2	87.2 – 99.5

* 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)#	1.75 ± 0.96	2.52 ± 4.74	-	-
C_{max} (ng/mL)	1695 ± 339 (1664)	1826 ± 374 (1790)	92.9	85.9 – 100.6
AUC_{0-72h} (ng.h/mL)	21821 ± 3900 (21445)	24020 ± 7798 (23117)	92.8	86.9 – 99.1

* geometric mean; # median (range)

The results of the study show that the preset acceptance limits of 80 -125 % are met by both AUC and C_{max} values regarding sulfamethoxazole and trimethoprim. Accordingly, the test Sulfamethoxazole/Trimethoprim 800mg/160mg FDC tablet meets the criteria for bioequivalence with regard to the rate and extent of absorption and is therefore bioequivalent to the reference formulation Septrin Forte® (Aspen Pharma Trading Limited).

4. Summary of Product Safety and Efficacy

[HA691 trade name] has been shown to conform to the same relevant standards of quality, efficacy and safety as those required of the WHO-recommended comparator product.

According to the submitted data on quality and bioavailability, [HA691 trade name] is pharmaceutically and therapeutically equivalent and thus interchangeable with the WHO recommended comparator products Septrin Forte® 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 lead to an acceptable clinical performance [HA691 trade name] is used in accordance with the SmPC.

Bioequivalence

[HA691 trade name] has shown to be bioequivalent with Septrin Forte ® (Aspen Pharma Trading Limited, Ireland).

Efficacy and Safety

Regarding clinical efficacy and safety, [HA691 trade name] 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 [HA691 trade name] was acceptable for the following indication: **"for the treatment and prevention of infections susceptible to sulfamethoxazole/trimethoprim in patients with HIV infection",** and has advised that the quality, efficacy and safety of [HA691 trade name] allow inclusion of [HA691 trade name], manufactured at Milan Laboratories (India) Pvt Ltd, Plot No. 35/36/63/64/65/67, Jawahar Coop Industrial Estate Ltd, Kamothe, Panvel, Navi Mumbai, Maharashtra 410 209, India in the list of prequalified medicinal products.