THE UNITED REPUBLIC OF TANZANIA

MINISTRY OF HEALTH

TANZANIA MEDICINES AND MEDICAL DEVICES AUTHORITY

PUBLIC ASSESSMENT REPORT FOR WIMAL 500/25 (SULFADOXINE AND PYRIMETHAMINE 500 MG / 25 MG) DISPERSIBLE TABLETS

Version number 1.0
21 August, 2023

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1. Introduction

WIMAL 500/25 dispersible tablets is an antimalarial medicinal product containing the active substances Sulfadoxine and Pyrimethamine. The reference product is “Fansidar® (sulphadoxine/pyrimethamine) Tablets 500 mg/25 mg’’ by AkaciaTM HealthCare (Pty) Limited, South Africa. Pyrimethamine is a diaminopyrimidine. It exerts its antimalarial activity by inhibiting plasmodial dihydrofolate reductase thus indirectly blocking the synthesis of nucleic acids in the malaria parasite. It is a slow-acting blood schizontocide and is also possibly active against pre-erythrocytic forms of the malaria parasite and inhibits sporozoite development in the mosquito vector. It has in vitro activity against the four long-established human malaria parasites. There has been rapid emergence of clinical resistance.

Sulfadoxine is a sulfonamide. Sulfonamides are competitive antagonists of p-aminobenzoic acid. They are competitive inhibitors of dihydropteroate synthase, the enzyme in P. falciparum, which is responsible for the incorporation of p-aminobenzoic acid in the synthesis of folic acid. Therefore, by acting at a different step in folate synthesis, sulfadoxine increases the effect of pyrimethamine. WIMAL 500/25 dispersible tablets is approved in Tanzania for use in all ages.

Product details

Registration number	TAN 23 HM 0290
Brand name	WIMAL 500/25
Generic name, strength, and form	Each dispersible tablet contains 25 mg pyrimethamine and 500 mg sulfadoxine
ATC classification	ATC Code: Pyrimethamine combinations. ATC code P01BD51
Distribution category	POM
Country of origin	Kenya
Associated product	N/A
Marketing Authorization Holder	Universal Corporation Limited, Club Road, Plot No. 13777, P.O. Box 1748 – 00902, Kikuyu Kenya
Local Technical Representative	Moraf Pharmaceutical Ltd, P.O. Box 21323, Dar es Salaam

1.1 Assessment procedure

The application for registration of WIMAL 500/25 was submitted on 15/09/2021. The product underwent full assessment. Assessment was completed in 3 (three) rounds of evaluation and the product was registered on 01/06/2023.

1.2 Information for users

Visual description of the finished product	Pink, round shape flat bevel edged tablet scored on one side and plain on reverse
Primary packing material	Alu/PVDC blisters
Secondary packing materials	Printed carton box
Shelf-life and storage condition	24 months, Do not store above 30°C, Protect from light and moisture
Route of administration	Oral
Therapeutic indications	Sulfadoxine and pyrimethamine dispersible tablets are used to prevent malaria in pregnant women as of week 13 of pregnancy and it can also be for prevention in children aged less than 12 months.

2. Labelling and product information

Summary of product characteristics
The SmPC included all the relevant information to ensure correct and safe use of the medicine by healthcare providers. The complete SmPC can be accessed here.

Package insert/leaflet
The package insert is confirmed to be derived from the SmPC and contains sufficient data for the end user. Since the product is POM, the package insert contains full prescribing information as per SmPC.

Container labels
The product label information is presented in English. Details in the secondary pack label include:

Brand name: WIMAL 500/25

Composition: Each dispersible tablet contains 25 mg pyrimethamine and 500 mg sulfadoxine

Pack size: 10 x 3's, 30 x 3's, 50 x 3's, 100 x 3's tablets

Manufacturing details: batch number, manufacturing date, and expiry date

Storage conditions: Do not store above 30°C, Protect from light and moisture

Manufacturer address: Physical address of release site

Unique identifier: Not applicable

Special warnings/precautions or instructions for use: Product contains lactose monohydrate

The details of the primary pack include:

Brand name and strength: WIMAL 500/25

Manufacturing details: batch number, manufacturing date and expiry date

Name of manufacturer: Universal Corporation Limited

The content of the primary and secondary labels was aligned to the requirements of the Part V of the Compendium: Guidelines on Format and Content of Product Labels for Medicinal products. The label contains sufficient information for proper identification of the medicine and post marketing follow up of the product.

Mock labels are appended as annex I.

3. Scientific discussion

Quality of Active Pharmaceutical Ingredients

Information on quality of the API was submitted in form of WHO Prequalification proof.

A. Sulfadoxine from Anuh Pharma Ltd

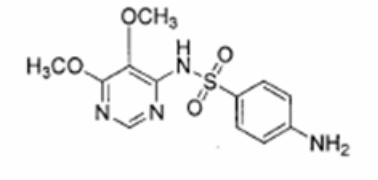
General Information

Sulfadoxine API is compendia in Ph.Int.

Molecular formula: $C_{12}H_{14}N_4O_4S$

Chemical name:
4-amino-N-(5,6-dimethoxy-4-pyrimidinyl) benzene sulfonamide

Structure:



General properties

Sulfadoxine is a white to creamy white powder slightly soluble in ethanol (95 %) and in methanol. Practically insoluble in ether and water at temperature 25°C ± 2°C. Base on solubility data provided shows that sulfadoxine is low soluble drug substance and exhibit pH dependent solubility, therefore particle size and distribution is considered to be critical and test and limit for this parameter are included in the final API specifications.

Manufacture

Sulfadoxine API manufacturer is Anuh Pharma Ltd. Manufacturing Block – AB-3, E-18, E-17/3 & 17/4, M.I.D.C, Tarapur, Boisar, Dist. Thane-401506, India. The manufacturing complies with GMP requirements as evidenced by the GMP certificate issued by the WHO. Sulfadoxine API is manufactured by chemical synthesis using conventional techniques. Sufficient controls of quality of materials and in-process checks were employed throughout the manufacturing process.

Specifications

The API specifications were set as per Ph. Int. standards and ICHQ3A. The parameters monitored during quality control are: Appearance, Solubility, Melting Range, Identification, Appearance of solution, Acidity, Loss on drying, Sulfated ash, Assay, Residual solvents, Particle Size. Compliance to these specifications were established via batch analysis data and stability studies.

Stability and container closure system

The re-test period of Sulfadoxine API is 36 months when packed in Polyethylene Bag stored in HDPE drum with storage condition 'Store at a temperature not exceeding 30°C, in a well closed container protected from light and moisture'.

B. Sulfadoxine from Mangalam Drugs & Organics Ltd

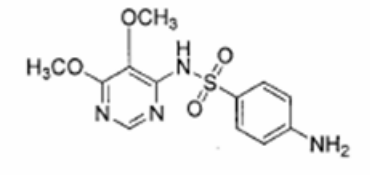
General Information

Sulfadoxine API is compendia in Ph.Int.

Molecular formula: $C_{12}H_{14}N_4O_4S$

Chemical name:
4-amino-N-(5,6-dimethoxy-4-pyrimidinyl) benzene sulfonamide

Structure:



General properties

Sulfadoxine is a white to creamy white powder slightly soluble in ethanol (95 %) and in methanol. Practically insoluble in ether and water at temperature 25°C ± 2°C. Base on solubility data provided shows that sulfadoxine is low soluble drug substance and exhibit pH dependent solubility, therefore particle size and distribution is considered to be critical and test and limit for this parameter are included in the final API specifications.

Manufacture

Sulfadoxine API manufacturer is Mangalam Drugs and Organics Ltd, Unit-2, Plant 2B, Plot No. 1203, GIDC., Vapi, 396 195, Gujarat, India. The manufacturing complies with GMP requirements as evidenced by the GMP certificate issued by the WHO. Sulfadoxine API is manufactured by chemical synthesis using conventional techniques. Sufficient controls of quality of materials and in-process checks were employed throughout the manufacturing process.

Specifications

The API specifications were set as per Ph. Int. standards and ICHQ3A. The parameters monitored during quality control are: Appearance, Solubility, Melting Range, Identification, Clarity and color of solution, Acidity, Loss on drying, Chlorides, Sulfated ash, Assay, Residual solvents, Particle Size. Compliance to these specifications were established via batch analysis data and stability studies.

Stability and container closure system

The re-test period of Sulfadoxine API is 36 months when packed in Polyethylene Bag stored in HDPE drum with storage condition 'Do not store above 30°C, protect from moisture, protect from light'.

C. Pyrimethamine from Mangalam Drugs and Organics Ltd

General Information

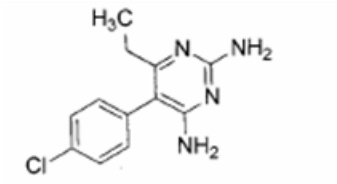
Pyrimethamine API is compendia in Ph.Int.

Molecular formula: $C_{12}H_{13}ClN_4$

Chemical name:

5-(4-chlorophenyl)-6-ethyl-2, 4-pyrimidinediamine

Structure:



General properties

Pyrimethamine is a white to off white, crystalline powder and practically insoluble in Water; slightly soluble in Ethanol (95 %) and Acetone. Base on solubility data provided shows that pyrimethamine is low soluble drug substance and exhibit pH dependent solubility, therefore

particle size and distribution is considered to be critical and test and limit for this parameter are included in the final API specifications.

Manufacture

Pyrimethamine API manufacturer is Mangalam Drugs and Organics Ltd, Unit-2, Plant 2B, Plot No. 1203, G.I.D.C., Vapi, 396 195 Gujarat, India.The manufacturing complies with GMP requirements as evidenced by the GMP certificate issued by the WHO. Pyrimethamine API is manufactured by chemical synthesis using conventional techniques. Sufficient controls of quality of materials and in-process checks were employed throughout the manufacturing process.

Specifications

The API specifications were set as per in-house standards and ICHQ3A. The parameters monitored during quality control are: Appearance, Solubility, Melting Range, Identification, Clarity and colour of solution, Acidity, Related substances, Chlorides, Loss on drying, Sulfated ash, Assay, Particle Size, Residual solvents. Compliance to these specifications were established via batch analysis data and stability studies.

Stability and container closure system

The re-test period of Pyrimethamine API is 48 months when packed in double LDPE bags (primary is transparent and secondary is black) followed by HDPE drum with storage condition ‘Do not store above 30°C, Protect from light’.

Quality of the Finished Pharmaceutical Product

Formulation

WIMAL 500/25 is a pink, round shape flat bevel edged tablet, Scored on one side and plain on the reverse.

WIMAL 500/25 contains the Sulfadoxine and Pyrimethamine other ingredients listed here after: Lactose monohydrate, Maize Starch, Povidone, Microcrystalline cellulose, Silica colloidal anhydrous, Sodium bicarbonate, Croscarmellose sodium, Sucralose, Orange flavor (maize maltodextrin, Arabic gum (E414), waxy maize maltodextrin, butylated hydroxy anisole (BHA) E320), Erythrosine soluble color (Erythrosine, water, sodium chloride, sodium sulphate), Purified talc, and Magnesium stearate. The quantities of all ingredients are confirmed to be in line with the recommendations of Handbook of Pharmaceutical Excipients, 8th Edition in terms of function and quantities. Ingredient, Lactose monohydrate is of safety concern therefore appropriate warnings were included in the product label.

Manufacture

The finished product manufacturers are Universal Corporation Limited, Club Road, Plot No. 13777, P.O.BOX 1748 – 00902, Kikuyu, Kenya. The compliance of the sites to TMDA GMP standards was confirmed through site inspection on DD/MM/YYYY.

Specifications

The FPP is in-house. The manufacturer controls the quality of the finished product as per in-house standards and ICH requirements. The parameters monitored during quality control are: Description, Identification by APIs, Disintegration time, Friability, Uniformity of dosage units by weight variation, Uniformity of dosage units by content uniformity, Assay of APIs, Dissolution, Related Substances, Loss on drying, Fineness of dispersion, and microbiological limit. Compliance to the standard was established using batch analysis data and stability data.

Stability and container closure system

Stability studies were conducted on 3(three) batches of the finished product stored at 30 ± 2°C & RH: 75 ± 5% RH for 24 months and 40± 2°C & RH: 75% ± 5% RH for 6 months. Based on the stability data presented, the approved shelf-life is 24 months when stored in Opaque PVDC (174mm) /Aluminum foil unit dose blisters (166mm) pack with storage condition 'Do not store above 30^{o}C.Protect from light and moisture'.

Safety and efficacy information

Safety and efficacy of WIMAL 500/25 was established through bioequivalence trial.

BE trial report number BE/18/012 was submitted.
In case of BE:

Study title	An Open-Label, Balanced, Randomized, Single-Dose, Two-Treatment, Single-Period, Parallel, Oral Bioequivalence Study of Sulfadoxine/ Pyrimethamine 500 mg / 25 mg Dispersible Tablets with FANSIDAR® (Sulfadoxine/ Pyrimethamine) 500 mg / 25 mg Tablets of Akacia Healthcare (Pty) Ltd., 4 Brewery Street, Isando, Gauteng, 1609, South Africa in Healthy, Male and Non-Pregnant Female Adult, Human Subjects under Fasting Conditions
Study design	An open-label, balanced, randomized, two-treatment, single-period, parallel, single oral dose, bioequivalence study under fasting condition
Study site	<u>Clinical Facility (Name and full mailing address)</u> Raptim Research Ltd., Clinical Pharmacology Unit (Clinic and Pathology): A-226. Screening Facility (PAP-213);

	T.T.C., Industrial Area, Mahape M.I.D.C., Navi Mumbai – 400 701, India. <u>Clinical Laboratories (Name and full mailing address)</u> Raptim Research Ltd., A-226, T.T.C. Industrial Area, Mahape M.I.D.C., Navi Mumbai – 400701, India. And Clinitech Laboratory Pvt. Ltd. Shop No. 9,10,11,12, Dattatray Maharaj CHS, 1st Floor, Janta Sahakari Bank, Plot No. 6, Sector 8, Airoli, Navi Mumbai-400708, India. <u>Analytical Laboratories (Name and full mailing address)</u> Raptim Research Ltd., Bioanalytical Unit: A-242, T.T.C., Industrial Area, Mahape M.I.D.C., Navi Mumbai - 400 701, India. <u>Company performing pharmacokinetic/statistical analysis (Name and full mailing address)</u> Raptim Research Ltd., Biostatistical Unit: A-242, T.T.C., Industrial Area, Mahape M.I.D.C., Navi Mumbai - 400 701, India.
Study dates	Phase – Initiation – Completion Screening – 09/09/19 – 27/09/19 Clinical – 28/09/19 – 02/10/19 Bioanalysis (Pyrimethamine) – 05/10/19 – 18/10/19 Bioanalysis (Sulfadoxine) – 17/10/19 – 23/10/19 Pharmacokinetic and Statistics – 31/10/19 – 01/11/19
Primary objective	To assess whether the test product was bioequivalent to reference product based on the evaluation of Cmax and AUC0-72 for “Sulfadoxine and Pyrimethamine
Secondary objective	Descriptive statistics for pharmacokinetic (PK) parameter - Tmax. Assessment of safety and tolerability profile of test and reference products
Number of participants	Planned-36 subjects Enrolled-36 subjects Dosed-36 subjects

	Withdrawn - 00 subject Bio-sample analyzed -36 subjects Pharmacokinetic and statistical data analyzed – 36 subjects	
Monitored parameters	Tmax, Cmax, AUC0→t, AUC0→∞, AUC% Extrapolation Kel and T1/2	
Investigational medicinal products	Test Product	Reference product
	Strength: 500/25mg Batch number: 5805612 Expiry date: 11/2020	Strength: 500/25mg Batch number: Z1764 Expiry date: 10/2022
Analytical method	High Pressure Liquid chromatography – MS/MS – detector (LC-MS/MS) method was used for the determination of plasma concentrations of analyte	
Statistical method	SAS® PROC MIXED (SAS Institute Inc., USA) procedure	

Efficacy results are summarized as follows:

Sulfadoxine

Parameter	Test	Reference	% Ratio of geometric means	90 % Confidence interval	DF	CV (%)
AUC0-72 (hr.µg/mL)	4410.81	4345.24	101.51	97.23 - 105.98	90	12.48
Cmax (µg/mL)	78.02	76.24	102.34	96.55 - 108.48	90	16.94

Pyrimethamine

Parameter	Test	Reference	% Ratio of geometric means	90 % Confidence interval	DF	CV (%)
AUC0-72 (hr.ng/mL)	10787.06	10434.79	103.38	98.20 - 108.83	90	14.91
Cmax (ng/mL)	205.39	199.68	102.86	97.04 - 109.03	90	16.93

The acceptance limits of 80 – 125% are met by the AUC and Cmax values. Furthermore, the safety profile of the test product is similar to that of reference product. Therefore, Sulfadoxine/ Pyrimethamine 500 mg / 25 mg Dispersible Tablets is equivalent and interchangeable with FANSIDAR® (Sulfadoxine/ Pyrimethamine) 500 mg / 25 mg Tablets of Akacia Healthcare (Pty) Ltd., South Africa under acceptable in vivo experimental conditions.

4. Benefit-Risk Assessment and Conclusion

On basis of the data submitted, the current state of knowledge and compliance to Good Manufacturing Practice, the benefit of the product outweighs the risks associated with its use when used in accordance to the summary of product characteristics. WIMAL 500/25 is recommended for registration.

5. Post-approval updates

Variation applications

Reference number	Date submitted	Change requested	Recommendation	Granting date

Feedback from pharmacovigilance, post marketing surveillance and enforcement activities

Type of feedback	Impact	Response

Re-registration applications

Application for renewal of registration was submitted on <DDMMYYYY>. The application was finalized in <number> rounds of evaluation. The product was confirmed to still be compliant to the standards of quality, safety and efficacy, hence registration was renewed on <DDMMYYYY>.

PART 5: CHANGE HISTORY

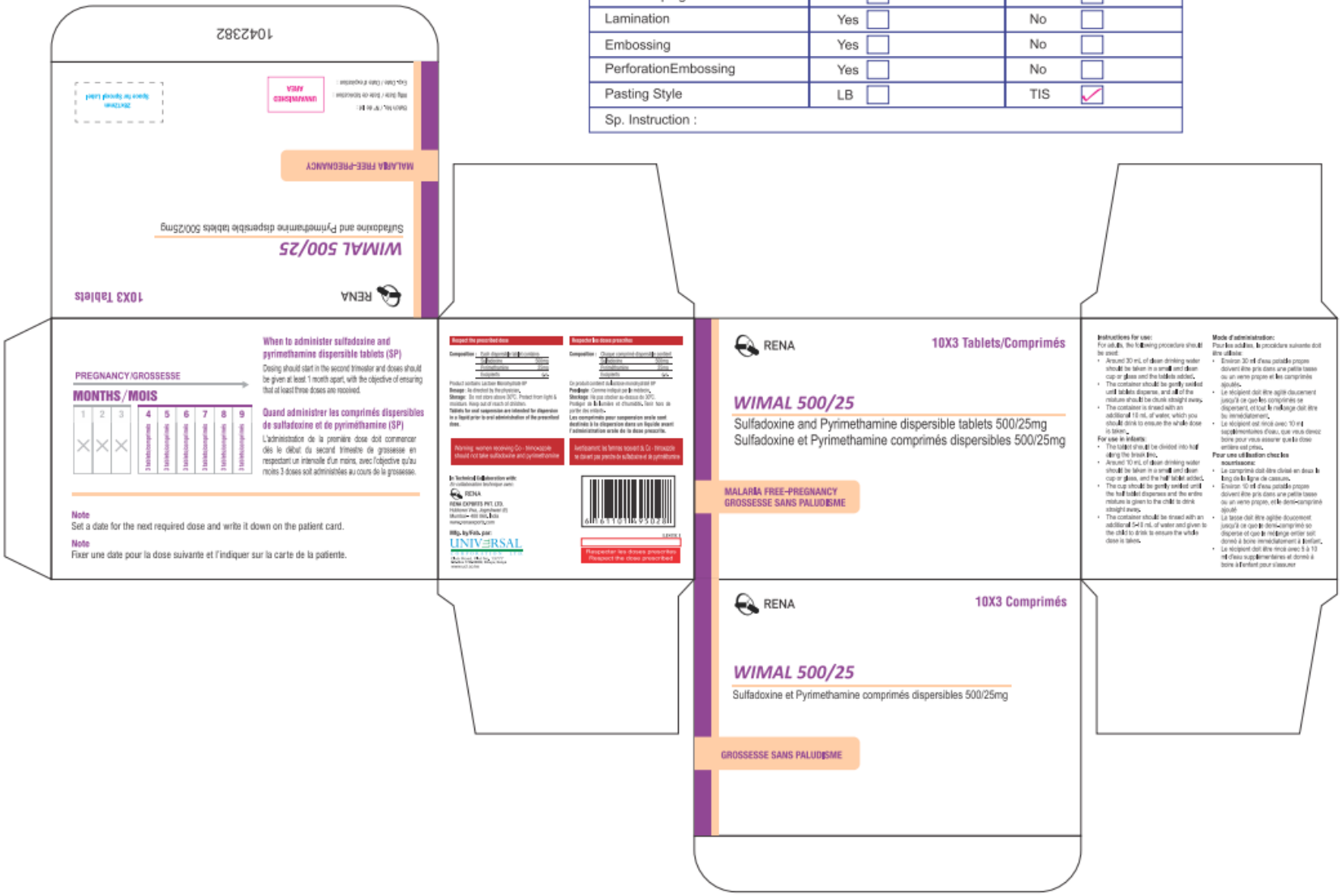
Version number	Date	Description of update	Section(s) Modified	Approval date

Annex I: Mock up labels;

Primary pack label;

Secondary pack label:

Foil Stamping	Yes ☐	No ☐
Lamination	Yes ☐	No ☐
Embossing	Yes ☐	No ☐
PerforationEmbossing	Yes ☐	No ☐
Pasting Style	LB ☐	TIS ☑
Sp. Instruction :		



Effective date: 03/10/2022