THE UNITED REPUBLIC OF TANZANIA

MINISTRY OF HEALTH

TANZANIA MEDICINES AND MEDICAL DEVICES AUTHORITY

PUBLIC ASSESSMENT REPORT FOR S-PYRIMAC (SULFADOXINE AND PYRIMETHAMINE 500 MG / 25 MG) DISPERSIBLE TABLETS

Version number 1.0
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1. Introduction

S-Pyrimac 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. S-Pyrimac dispersible tablets is approved in Tanzania for use in all ages.

Product details

Registration number	TAN 23 HM 0299
Brand name	S-Pyrimac
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	India
Associated product	N/A
Marketing Authorization Holder	Macleods Pharmaceuticals Limited 304, Atlanta Arcade, Marol Church road, Andheri (East), India
Local Technical Representative	RK Pharmaceitical (TZ) Limited Plot No.: 326, Dar es Salaam

1.1 Assessment procedure

The application for registration of S-Pyrimac was submitted on 12/08/2022. The product underwent abridged 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	White to off-white, capsule shaped, biconvex, uncoated tablet debossed with 'F' and '41' on either side of the break line on one side, and plain on the other side
Primary packing material	Alu/ Clear PVC/PVdC blister
Secondary packing materials	Printed carton box
Shelf-life and storage condition	24 months, Do not store above 30°C. Store tablets in blisters in the provided carton in order to protect from light
Route of administration	Oral
Therapeutic indications	Sulfadoxine 500 mg and Pyrimethamine 25 mg Dispersible Tablets is indicated for intermittent preventive treatment of malaria as part of antenatal care for women in their first or second pregnancy, in areas of moderate-to-high malaria transmission in Africa. Sulfadoxine 500 mg and Pyrimethamine 25 mg Dispersible Tablets is also indicated for intermittent preventive treatment of malaria in infants aged less than 12 months at the time of the second and third rounds of vaccination against diphteria, tetanus and pertussis and vaccination against measles, in areas of moderateto-high malaria transmission of Africa (annual entomological inoculation rate ≥ 10), where the combination of sulfadoxine and pyrimethamine is still effective (prevalence of the Pfdhps 540 mutation of ≤ 50%).

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: S-Pyrimac

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

Pack size: 10, 25, 50 or 100 tablets

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

Storage conditions: Do not store above 30°C. Store tablets in blisters in the provided carton in order to protect from light

Manufacturer address: Physical address of release site

Unique identifier: Not applicable

Special warnings/precautions or instructions for use:

The details of the primary pack include:

Brand name and strength: S-Pyrimac

Manufacturing details: batch number, manufacturing date and expiry date

Name of manufacturer: Macleods Pharmaceuticals 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

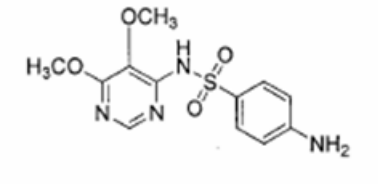
General Information

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 Macleods Pharmaceuticals Limited, Plot No. 2209, GIDC Industrial Estate, At and Post Sarigam, Taluka: Umbergaon, Valsad, Gujarat, ZIP Code: 396 155, 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: Description, solubility, identification by IR and HPLC, related substances, heavy metals, sulfates, chlorides, acidity, clarity and colour of solution, particle size (laser diffraction), loss on drying, assay, and residue solvents. Compliance to these specifications were established via batch analysis data and stability studies.

<u>Stability and container closure system</u>

The re-test period of Sulfadoxine API is 18 months when packed in LDPE bag with storage condition ‘Do not store above 30°C, Protect from light’.

B. Pyrimethamine

General Information

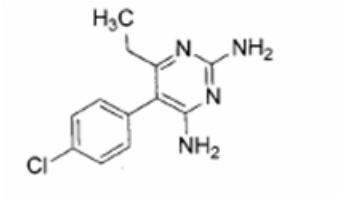
Pyrimethamine API is compendia in Ph.Int.

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 Macleods Pharmaceuticals Limited, Plot No. 2209, GIDC Industrial Estate, At and Post Sarigam, Taluka: Umbergaon, Valsad, Gujarat, ZIP Code: 396 155, 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 Ph. Int. standards and ICHQ3A. The parameters monitored during quality control are: Description, solubility, identification by IR, chloride, and melting range, related substances, heavy metals, sulfated ash, chlorides, acidity or alkalinity, particle size (laser diffraction), loss on drying, assay, and residue 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 18 months when packed in LDPE bag with storage condition ‘Do not store above 30°C, Protect from light’.

Quality of the Finished Pharmaceutical Product

Formulation

S-Pyrimac is a white to off white, capsule shaped, biconvex uncoated tablets debossed with 'F' and '41' on ethier side of breakline on one side and plain on other side

S-Pyrimac contains the Sulfadoxine and Pyrimethamine other ingredients listed here after: pregelatinized starch croscarmellose sodium colloidal silicon dioxide microcrystalline cellulose, aspartame, orange flavour, sodium stearyl fumarate. 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.

Manufacture

The finished product manufacturers are Macleods Pharmaceuticals Limited, Unit - II, Phase – II, Plot No.: 25 – 27, Survey No.: 366, Premier Industrial Estate, Kachigam, Daman – 396210, India. 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 HPLC and TLC, friability, hardness, disintegration time, water, fineness of dispersion, uniformity of dosage units, dissolution, assay, related substances, subdivision of tablets (by weight variation and content uniformity) 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 Alu-PVC/PVdC blisters pack with storage condition ‘Do not store above 30°C. Protect from light. Store tablets in the blisters in the provided carton’.

Safety and efficacy information

S-Pyrimac Tablet is already registered by WHO. Information on clinical data has been fully evaluated during the registration of the product (Refer: WHO pre-qualification reference Number MA159). In this context, re-assessment of this part is not considered as necessarily required.

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. S-Pyrimac 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: