THE UNITED REPUBLIC OF TANZANIA

MINISTRY OF HEALTH

TANZANIA MEDICINES AND MEDICAL DEVICES AUTHORITY

# PUBLIC ASSESSMENT REPORT FOR SULPHATRIM (TRIMETHOPRIM 40 MG/5 ML + SULFAMETHOXAZOLE 200 MG/5 ML) SUSPENSION

**Version number 1.0**
**21 August, 2023**

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## 1. Introduction

Sulphatrim suspension is a generic medicine of Co-Trimoxazole 40 mg/200 mg per 5 ml Paediatric Suspension of Aspen Pharma Trading Limited, Dublin, Ireland. Sulphatrim suspension is an antibacterial drug composed of two active principles, sulfamethoxazole and trimethoprim. Sulfamethoxazole is a competitive inhibitor of dihydropteroate synthetase enzyme. Sulfamethoxazole competitively inhibits the utilisation of para-aminobenzoic acid (PABA) in the synthesis of dihydrofolate by the bacterial cell resulting in bacteriostasis. Trimethoprim reversibly inhibits bacterial dihydrofolate reductase (DHFR), an enzyme active in the folate metabolic pathway converting dihydrofolate to tetrahydrofolate. Depending on the conditions the effect may be bactericidal. Thus, trimethoprim and sulfamethoxazole block two consecutive steps in the biosynthesis of purines and therefore nucleic acids essential to many bacteria. This action produces marked potentiation of activity in vitro between the two agents. Sulphatrim suspension is approved in Tanzania for use in children aged 12 years and under (infants (>6 weeks to <2 years old) and children (>2 to <12 years old).

**Product details**

| | |
|---|---|
| Registration number | TAN 23 HM 0247 |
| Brand name | Sulphatrim |
| Generic name, strength, and form | Each 5 ml contains 40 mg Trimethoprim and 200 mg Sulfamethoxazole |
| ATC classification | ATC Code: J01EE01<br>Pharmacotherapeutic group: Sulfonamide Antibiotic |
| Distribution category | POM |
| Country of origin | India |
| Associated product | N/A |
| Marketing Authorization Holder | Lincoln Pharmaceuticals Limited<br>Trimul Estate,Khantraj,Taluka: Kalol,District: Gandhinagar,Gujarat<br>India |
| Local Technical Representative | Heko Pharmacy Ltd.<br>Plot No.32/57, Sikukuu/Tandamti Street, Kariakoo,<br>P.O. Box 2657<br>Dar es Salaam |

### 1.1 Assessment procedure

The application for registration of Sulphatrim was submitted on 01/9/2020. The product underwent full assessment. Assessment was completed in 4 (four) 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 colour suspension |
| Primary packing material | 100 ml amber PET bottle |
| Secondary packing materials | Printed carton box |
| Shelf-life and storage condition | 36 months, Do not store above 30°C. |

| | |
|---|---|
| | Protect from light. |
| Route of administration | Oral |
| Therapeutic indications | Indicated in children aged 12 years and under (infants (>6 weeks to <2 years old) and children (> 2 to <12 years old) for the treatment of the following infections when owing to sensitive organisms<br>• Treatment and prevention of Pneumocystis jirovecii pneumonitis (PJP).<br>• Treatment and prophylaxis of toxoplasmosis.<br>• Treatment of nocardiosis.<br>The following infections may be treated with Co-Trimoxazole where there is bacterial evidence of sensitivity to Co-Trimoxazole and good reason to prefer the combination of antibiotics in Co-Trimoxazole to a single antibiotic.<br>• Acute uncomplicated urinary tract infection.<br>• Acute otitis media<br>• Acute exacerbation of chronic bronchitis |

## 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: Sulphatrim

Composition: Each 5 ml contains 40 mg Trimethoprim and 200 mg Sulfamethoxazole

Pack size: 100 mL

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

Storage conditions: Do not store above 30°C. Protect from light

Manufacturer address: physical address of release site

Unique identifier: Not applicable

Special warnings/precautions or instructions for use: Keep the bottle tightly closed. Shake well before use.

The details of the primary pack include:

Brand name and strength: Sulphatrim

Manufacturing details: batch number, manufacturing date and expiry date

Name of manufacturer: Lincoln 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 the quality of the APIs was submitted in form of DMFs.

**Trimethoprim**

**General Information**

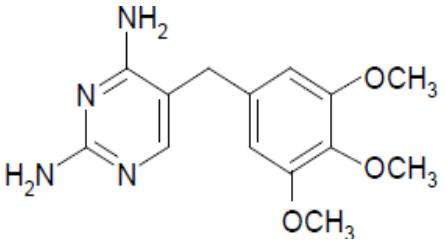
Trimethoprim API is compendia in USP, Ph.Eur., and BP.

Molecular formula: $C_{14}H_{18}N_4O_3$

Chemical name:

5-(3,4,5-Trimethoxybenzyl) pyrimidine-2,4-diamine

Structure:




**General properties**

The active substance is white or yellowish-white powder, very slightly soluble in water, slightly soluble in alcohol. The substance shows polymorphism. The manufacturer consistently produces the same polymorphic form.

Trimethoprim is a class II substance in the BCS classification system. It has a low aqueous solubility. Appropriate limits have been included in the active substance specifications to monitor the particle size and size distribution.

**Manufacture**

Trimethoprim API manufacturer is Andhra Organics Limited, Plot No.110A, IDA, Pydibhimavaram, Srikakulam – 532 409, India. The manufacturing complies with GMP requirements as evidenced by the GMP certificate issued by the Drugs Control Administration, Government of Andhra pradesh. Trimethoprim 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 BP standards and ICHQ3A. The parameters monitored during quality control are: Description, solubility, identity, appearance solution, particle size, residual solvents, assay, related impurities, loss on drying, sulphated ash, and heavy metal. Compliance to these specifications were established via batch analysis data and stability studies.

Stability and container closure system

The re-test period of Trimethoprim API is 60 months when packed in original container with storage condition ‘The product should be kept in airtight containers below 25°C’.

**Sulfamethoxazole**

**General Information**

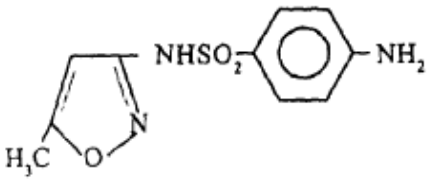
Sulfamethoxazole API is compendia in USP, Ph.Eur., and BP.

Molecular formula: $C_{10}H_{11}N_3O_3S$

Chemical name:

N'-(5-Methylisoxazole-3-yl) Sulfanilamide

Structure:




**General properties**

Sulfamethoxazole is a white or almost white, odourless, crystalline powder and is practically insoluble in water, freely soluble in acetone, sparingly soluble in alcohol, slightly soluble in ether. It dissolves in dilute solutions of sodium hydroxide. The manufacturer consistently produces the same polymorphic form.

Sulfamethoxazole is a class IV substance in the BCS classification system. It has a low aqueous solubility. Appropriate limits have been included in the active substance specifications to monitor the particle size and size distribution.

**Manufacture**

Sulfamethoxazole API manufacturer is Andhra Organics Limited, Plot No.110A, IDA, Pydibhimavaram, Srikakulam – 532 409, India. The manufacturing complies with GMP requirements as evidenced by the GMP certificate issued by the Drugs Control Administration, Government of Andhra pradesh. Sulfamethoxazole 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 BP standards and ICHQ3A. The parameters monitored during quality control are: Description, solubility, identity, appearance solution, particle size, assay, related impurities, loss on drying, sulphated ash, and heavy metal. Compliance to these specifications were established via batch analysis data and stability studies.

Stability and container closure system

The shelf-life period of Sulfamethoxazole API is 72 months when packed in original container with storage condition 'The product should be kept in airtight containers below 30°C'.

## Quality of the Finished Pharmaceutical Product

### Formulation

Sulphatrim is a white to off white coloured suspension.

Sulphatrim contains the Trimethoprim and Sulfamethoxazole and other ingredients listed here after: sodium methyl hydroxy benzoate, sodium propyl hydroxy benzoate, disodium edetate, carmellose sodium, sucrose, citric acid monohydrate, sodium citrate, aspartame, polysorbate 80 (Tween 80), Ess. mixed fruit, purified water. 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 manufacturer is Lincoln Pharmaceuticals Limited, Trimul Estate, Khatraj, Tal. Kalol, Dist. Gandhinagar, Gujarat, India. The compliance of the sites to TMDA GMP standards was confirmed through site inspection on DD/MM/YYYY

### Specifications

The FPP is compendia in USP. 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 (TLC and IR), deliverable volume, uniformity of dosage unit (by content uniformity), acidity, suspendability, assays of APIs and preservative agents, dissolution, related impurities, and microbial purity. 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 36 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 HDPE bottle with desiccant with storage condition ‘Do not store above 30°C. Protect from light.’

### Safety and efficacy information

Safety and efficacy of Sulphatrim was established through a bioequivalence trial.

BE trial report number C17437 was submitted.

| | |
|---|---|
| Study title | A Randomized, Two-Way Crossover, Open Label, Balanced, Two-Treatment, Two-Period, Two-Sequence, Single Dose, Oral Bioequivalence Study for Paediatric Co-Trimoxazole OralSuspension BP (240 mg/5 mL) of Lincoln Pharmaceuticals Ltd. India with Bactrim® Oral Suspension Containing Trimethoprim 40 mg and Sulfamethoxazole 200 mg (240 mg/5 mL) of Roche |

| | | |
|---|---|---|
| | Farmaceutica Quimica Lda., Amadora, Portugal., in 24 healthy, adult, male, human subjects under fasting conditions | |
| Study design | Comparative randomized, two-way crossover, open label, balanced, two-treatment, two-period, two-sequence, cross over under fasting condition | |
| Study site | Om Sai Clinical Research Pvt. Ltd,<br>C.S.T.No. 379/1-6, Karnal Chowki, Perth Bhag, Sangli-416416, Maharashtra, India | |
| Study dates | Clinical: Period 1 12/07/2019 to 14/07/2019 and Period 2: 19/07/2019 to 21/07/2019<br><br>Bioanalytical: 26/07/2019 to 09/08/2019 | |
| Primary objective | The study was designed to compare the rate, extent of absorption and safety of Test Product (B): Paediatric Co-Trimoxazole Oral Suspension BP (240 mg/5 mL) containing Trimethoprim 40 mg and Sulfamethoxazole 200 mg of Lincoln Pharmaceuticals Ltd. India.and the single dose of corresponding Reference Product (A): Bactrim® Oral Suspension Containing Trimethoprim 40 mg and Sulfamethoxazole 200 mg (240 mg/5 mL) of Roche Farmaceutica Quimica Lda., Amadora,Portugal in 24 Normal healthy subjects under fasting conditions | |
| Secondary objective | To monitor the safety and tolerability of a single dose of Paediatric Co-Trimoxazole Oral Suspension BP (240 mg/5 mL) when administered in 24 healthy human male subjects under fasting condition | |
| Number of participants | Planned-24 subjects<br>Enrolled-24 subjects<br>Dosed-24 subjects<br>Withdrawn - 00 subject<br>Bio-sample analyzed -24 subjects<br>Pharmacokinetic and statistical data analyzed – 24 subjects | |
| Monitored parameters | Tmax, Cmax, AUC0→t, AUC0→∞, AUC% Extrapolation Kel and T1/2 | |
| Investigational medicinal products | Test Product | Reference product |
| | Strength: Trimethoprim 40 mg and Sulfamethoxazole 200 mg (240 mg/5 mL)<br>Batch number: CO9074<br>Expiry date: 04/2022 | Strength: Trimethoprim 40 mg and Sulfamethoxazole 200 mg (240 mg/5 mL)<br>Batch number: F0991F02<br>Expiry date: 02/2020 |
| 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 software version 9.2 | |

Efficacy results are summarized as follows:

Sulfamethoxazole

| PK Parameter | $LnC_{max}$ (µg/mL) | $LnAUC_{0-t}$ (µg*hr/mL) | $LnAUC_{0-inf}$ (µg*hr/mL) |
|---|---|---|---|
| Confidence interval | 95.261-100.886 | 93.241-106.851 | 92.304-104.139 |
| Acceptance Criteria | 80-125% | 80-125% | 80-125% |

**Sulfamethoxazole**

| Pharmacokinetic Parameters | Test Product (B) N=24 | Reference Product (A) N=24 |
|---|---|---|
| $C_{max}$ (µg/mL) | 23.35 | 23.83 |
| $AUC_{0-t}$ (µg × hr/mL) | 164.887 | 165.132 |
| $AUC_{0-inf}$ (µg × hr/mL) | 184.307 | 187.902 |

Trimethoprim

| PK Parameter | $LnC_{max}$ (µg/mL) | $LnAUC_{0-t}$ (µg*hr/mL) | $LnAUC_{0-inf}$ (µg*hr/mL) |
|---|---|---|---|
| Confidence interval | 98.531-101.053 | 82.015-100.053 | 84.342-100.027 |
| Acceptance Criteria | 80-125% | 80-125% | 80-125% |

**Trimethoprim**

| Pharmacokinetic Parameters | Test Product (B) N=24 | Reference Product (A) N=24 |
|---|---|---|
| $C_{max}$ (µg/mL) | 0.79 | 0.79 |
| $AUC_{0-t}$ (µg × hr/mL) | 4.361 | 4.720 |
| $AUC_{0-inf}$ (µg × hr/mL) | 5.217 | 5.615 |

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, Paediatric Co-Trimoxazole (Sulphatrim) Oral Suspension BP (240 mg/5 mL) containing Trimethoprim 40 mg and Sulfamethoxazole 200 mg of Lincoln Pharmaceuticals Ltd. India is equivalent and interchangeable with Bactrim® Oral Suspension containing Trimethoprim 40 mg and Sulfamethoxazole 200 mg (240 mg/5 mL) of Roche Farmaceutica Quimica Lda., Amadora,Portugal 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. Sulphatrim 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: