THE UNITED REPUBLIC OF TANZANIA

MINISTRY OF HEALTH

TANZANIA MEDICINES AND MEDICAL DEVICES AUTHORITY

PUBLIC ASSESSMENT REPORT FOR COTRIKANT-960 (SULFAMETHOXAZOLE 800MG AND TRIMETHOPRIM 160MG) TABLETS

Version number 1
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1. Introduction

Cotrikant-960 is a generic medicine of Septrin forte tablets of Aspen Pharma Trading Limited, Dublin, Ireland. Cotrikant-960 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. Cotrikant-960 is approved in Tanzania for use in adults and children (>12 to <18 years old) and adults (>18 years old).

1.1 Product details

Registration number	TAN 21 HM 0440
Brand name	Cotrikant-960
Generic name, strength, and form	Each tablet contains Sulfamethoxazole 800mg and trimethoprim 160mg
ATC classification	Antibacterials for systemic use, combinations of sulfonamides and trimethoprim (sulfamethoxazole and trimethoprim: J01EE01)
Distribution category	POM
Country of origin	India
Associated product	N/A
Marketing Authorization Holder	S K Age Exports, 3 A Shiv Sagar Estate, Dr. Annie Besant Road, Worli, India
Local Technical Representative	Phillips Distributors Ltd, Plot No. 12D (Behind DHL office), Nyerere Road, P. O. Box 737, Dar es Salaam, Tanzania

1.2 Assessment procedure

The application for registration of Cotrikant-960 was submitted in 2014. The product underwent full assessment. Assessment was completed in 3 (three) rounds of evaluation and the product was registered on 09 October 2021.

1.3 Information for users

Visual description of the finished product	White coloured, uncoated, oval shaped, biconvex tablet having central break line on

	one side and plain on other side
Primary packing material	Alu/Alu Blister
Secondary packing materials	A printed carton box
Shelf-life and storage condition	36 months, Do not store above 30°C. Protect from moisture
Route of administration	Oral
Therapeutic indications	Co-trimoxazole should only be used where, in the judgement of the physician, the benefits of treatment outweigh any possible risks; consideration should be given to the use of a single effective antibacterial agent. The in vitro susceptibility of bacteria to antibiotics varies geographically and with time; the local situation should always be considered when selecting antibiotic therapy. 1) Treatment and prophylaxis (primary and secondary) of Pneumocytosis jiroveci (P. carinii) in adults and children. 2) Treatment and prophylaxis of toxoplasmosis, treatment of nocardiosis. 3) Treatment of urinary tract infections and acute exacerbations of chronic bronchitis, where there is bacterial evidence of sensitivity to Co-trimoxazole and good reason to prefer this combination to a single antibiotic. 4) Treatment of acute otitis media where there is good reason to prefer Co-trimoxazole to a single antibiotic.

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: Cotrikant-960

Composition: Each tablet contains Sulfamethoxazole 800mg and trimethoprim 160mg

Pack size: 10x10 tablets

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

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

Manufacturer address: physical address of release site

Unique identifier: Not applicable

Special warnings/precautions or instructions for use: N/A

The details of the primary pack include:

Brand name and strength: Cotrikant-960
Manufacturing details: batch number, manufacturing date and expiry date

Name of manufacturer: S Kant Healthcare Ltd,

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

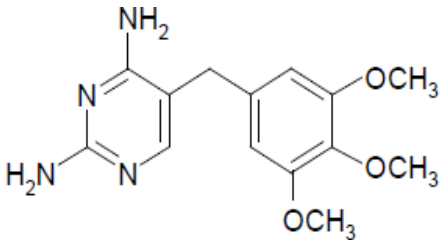
Trimethoprim API is compendia in USP, Ph.Eur., and BP.

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 polymorphism, 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, polymorphism, 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

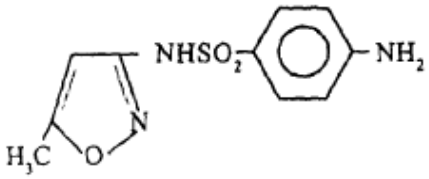
Sulfamethoxazole API is compendia in USP, Ph.Eur., and BP.

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

Cotrikant-960 is a white coloured, uncoated, oval shaped, biconvex tablet having central break line on one side and plain on other side.

Cotrikant-960 contains the Sulfamethoxazole and Trimethoprim and other ingredients listed here after: Maize Starch, Docusate Sodium, Sodium Starch Glycolate, Magnesium Stearate, Colloidal Anhydrous Silica, Purified Talc, 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 manufacturers are S Kant Healthcare Ltd, Plot No. 1802-1805, G.I.D.C, Phase III, Vapi- 396 195, Gujarat, India. The compliance of the sites to TMDA GMP standards was confirmed through site inspection on DD/MM/YY.

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), average weight, length, breadth, thickness, friability, weight variation, hardness, assay, disintegration, dissolution, uniformity of weight, 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 a 6(six) 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 36 months when stored

in Alu/Alu blister with storage condition ‘Do not store above 30°C. Protect from moisture’.

Safety and efficacy information

Safety and efficacy of Cotrikant-960 was established through bioequivalence trial.

BE trial report number SKH/COTR/002/14 was submitted.

In case of BE:

Study title	A single dose, randomized, two sequence, two treatments, two-way crossover study to assess bioequivalence of Co-trimoxazole tablets BP 960mg of S. Kant Healthcare Ltd. and “Septrin forte tablets” of Aspen Pharma Trading Limited, Dublin, Ireland in Healthy adult male human subjects under fasted condition	
Study design	Randomized, open label, balanced, two-treatment, two-period, two sequence, single dose, crossover design BE study in normal, healthy, adult, male human subjects under fasting conditions	
Study sites	L.T.M.M College & Hospital, Sion, Mumbai, India	
Study dates	03/02/2014 to 12/02/2014	
Primary objective	To compare the rate and extent of absorption of the two formulations Co-Trimoxazole tablets BP 960mg of S. Kant Healthcare Ltd and Septrin forte tablets” of the Aspen Pharma Trading Limited, Dublin, Ireland in healthy adult male human subjects	
Secondary objective	To monitor the safety of the two formulations Co-Trimoxazole tablets BP 960mg of S. Kant Healthcare Ltd and “Septrin forte tablets” of Aspen Pharma Trading Limited, Dublin, Ireland in healthy adult male human subjects	
Number of participants	A total of 24 subjects were dosed in Period-I and II. None of the subject was discontinued from the study. Hence, a total of 24 subjects completed the clinical phase successfully. The data of 24 subjects were analysed for PK and safety of the study products	
Monitored parameters	Tmax, Cmax, AUC0→t, AUC0→∞, AUC% Extrapolation Kel and T1/2	
Investigational medicinal	Test Product	Reference product

products	Strength: 960 mg Batch number: CG3002 Expiry date: Nov 2016	Strength: 960 mg Batch number: G1474 Expiry date: Dec/2015
Analytical method	LC-MS/MS method was used for the determination of plasma concentration of analyte	
Statistical method	ANOVA and 90% confidence interval for the ratio of the population means for log-transformed pharmacokinetic parameters Cmax, AUC0-t, and AUC0-∞ were performed	

Efficacy results are summarized as follows:

Parameter	Test	Reference	% Ratio of geometric means	90 % Confidence interval	DF	CV (%)
AUC0-t (units)	Fill	Fill	Fill	Fill	Fill	Fill
AUC0-inf (units)	Fill	Fill	Fill	Fill	Fill	Fill
Cmax (units)	Fill	Fill	Fill	Fill	Fill	Fill

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, Cotrikant-960 is equivalent and interchangeable with Septrin forte tablets 960 mg of Aspen Pharma Trading Limited, Dublin 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. Cotrikant-960 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

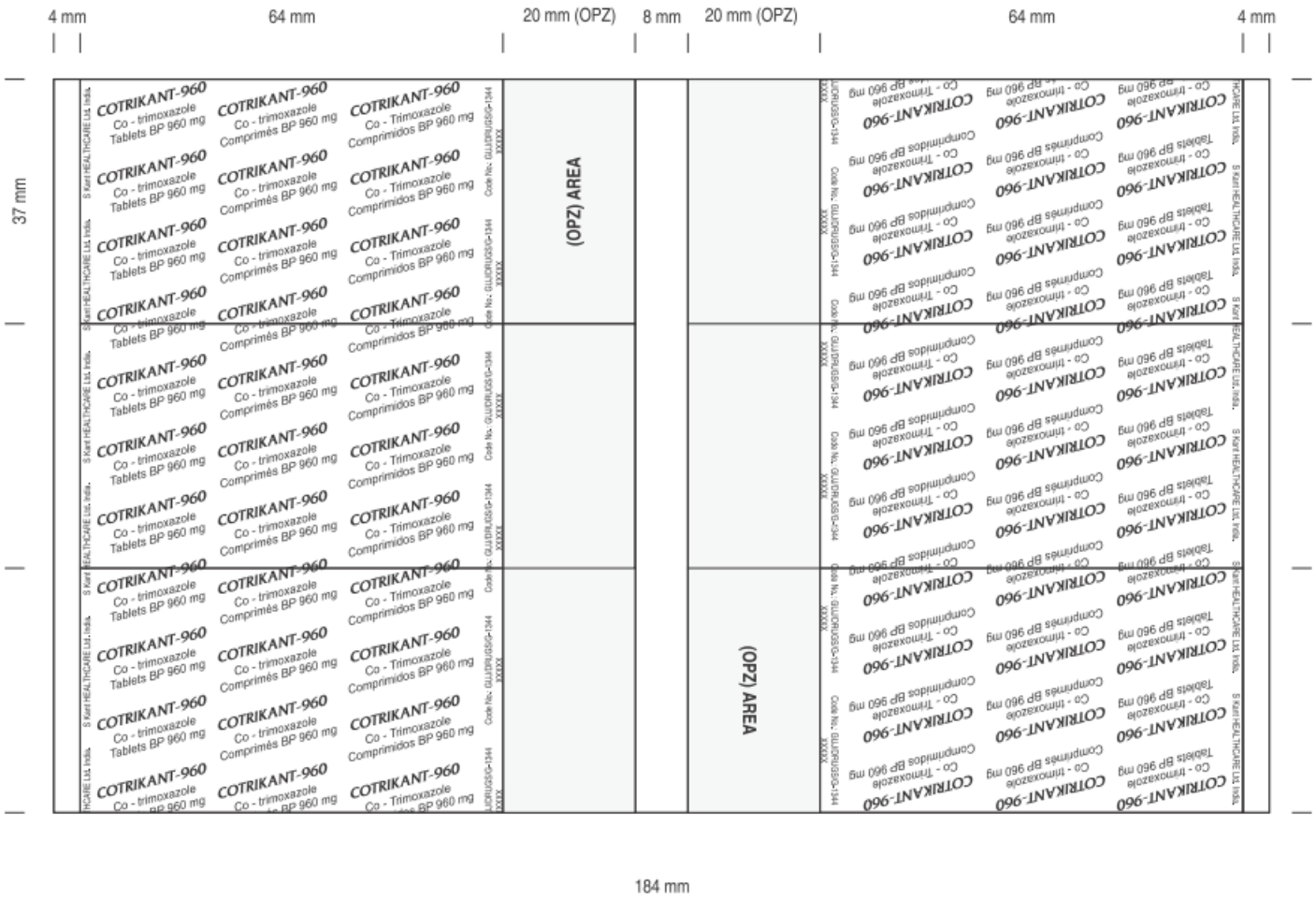
Application for renewal of registration was submitted on <DDMMYYYY>. The application was finalized in <number> rounds of evaluation. The product was confirmed to still be compliant to the standards of quality, safety and efficacy, hence registration was renewed on <DDMMYYYY>.

PART 5: CHANGE HISTORY

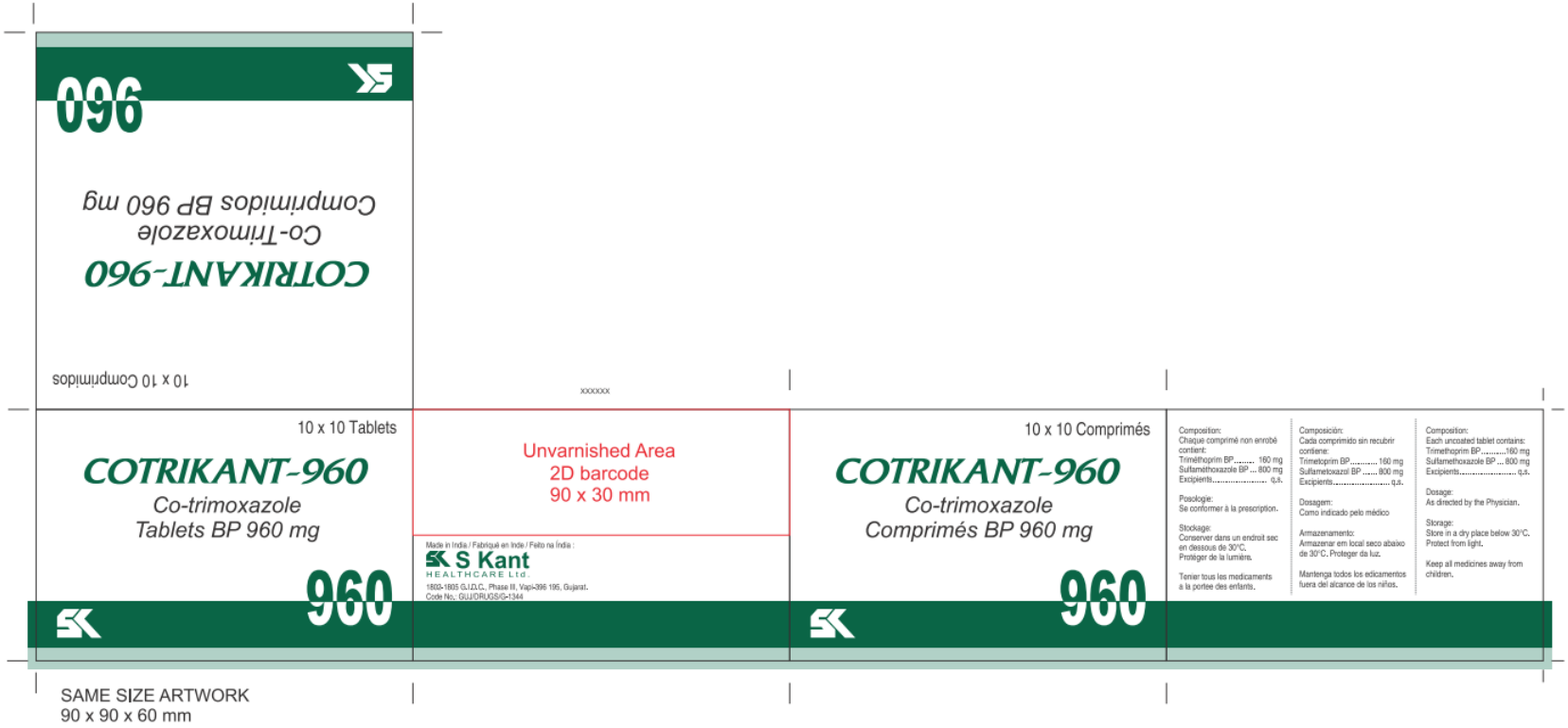
Version number	Date	Description of update	Section(s) Modified	Approval date

Annex I: Mock up labels;

Primary pack label;



Secondary pack label;



Effective date: 03/10/2022