TANZANIA MEDICINES AND MEDICAL DEVICES AUTHORITY

PUBLIC ASSESSMENT REPORT FOR SPINO-25 (SPIRONOLACTONE 250 MG) FILM COATED TABLETS

Version number 0.1,

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1. Introduction

Spino-25 is a generic medicine of spironolactone. Spino-25 is a potassium-sparing diuretic medicine belonging to aldosterone antagonist group. Spino-25 exerts is activity by competitively binding to receptors at the aldosterone-dependent sodium-potassium exchange site in the distal convoluted renal tubule. This increases the excretion of sodium and water while retaining potassium. Spino-25 is approved in Tanzania for use in all age groups; however, the use in children requires guidance from a pediatric specialist.

1.1 Product details

Registration number	TAN 21 HM 0129
Brand name	Spino-25
Generic name, strength and form	Spironolactone 25 mg tablet
ATC classification	CO3DA01
Distribution category	Prescription Only Medicine
Country of origin	India
Associated product	Nil
Marketing Authorization Holder	Resonant Pharmaceuticals Private Limited
Local Technical Representative	Heko Pharmacy Limited

1.2 Assessment procedure

The application for registration of Spino-25 was submitted on 26/06/2019. The product underwent full assessment. Assessment was completed in three (3) rounds of evaluation. Spino-25 was registered on 29/03/2021.

1.3 Information for users

Visual description of the finished product	White, round, biconvex, film coated tablets
Primary packing material	Aluminium/PVC blisters of 10's
Secondary packing materials	10 blisters in a carton box
Shelf-life and storage condition	Store below 30^{o}C
Route of administration	Per oral
Therapeutic indications	Treatment of hypertension, heart failure and hypokalemia

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 that is intended for long term use, the package insert contains simplified information for patients.

Container labels

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

Brand name: Spino-25

Composition: Spironolactone 25 mg and excipients including lactose

Pack size: 10 x 10's

Manufacturing details: batch number, manufacturing date, expiry date

Storage conditions: Store below 30^{O}C. Protect from light and moisture

Manufacturer address: Brawn Laboratories Limited, 13, N.I.T., Industrial Area, Fariadabad-12100, Haryana, India.

Unique identifier: TMDA registration number

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

The details of the primary pack include:
Brand name and strength: Spino-25

Manufacturing details: batch number, manufacturing date and expiry date

Name of manufacturer: Brawn Laboratories 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.
Describe any approved deviation to the requirements and the justification for the deviation.

Mock labels are <appended as annex I >.

3. Scientific discussion

Quality of Active Pharmaceutical Ingredient(s)

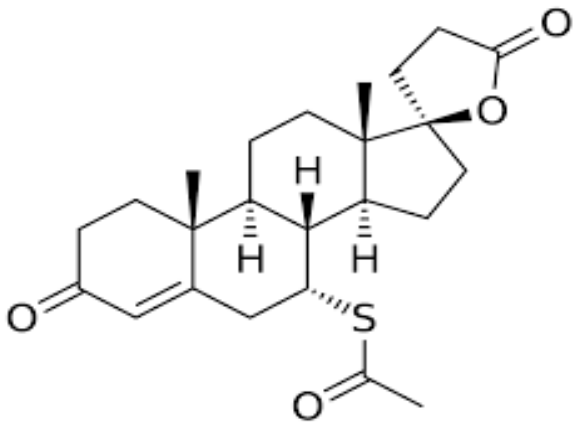
Information on quality of the API was submitted in form of full details as per Compendium requirements.

General properties
<Spironolactone> API is compendia in USP and European Pharmacopeia.

Molecular formula: $C_{24}H_{32}O_4S$

Chemical name: 7α-Acetylthio-17α-hydroxy-3-oxopregn-4-ene-21-carboxylic acid γ-lactone

Structure:



Critical physico-chemical properties of the API include low solubility (BCS class 2) thus particle size was a critical parameter.

Manufacture

The API manufacturing site, Zhejiang Xinhu Pharmaceutical Company Limited, 7-1 Donghai 3rd Ave, Linhai Shi, Taizhou Shi, Zhejiang Sheng, China was noted to comply with WHO GMP requirements as evidenced by the GMP certificate issued by the Guangdong Food and Drug Administration. Spironolactone 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 USP standards and ICHQ3A. The parameters monitored during quality control are: appearance, solubility, identification, limit of mercapto compounds and related substances (impurity I, impurity E, impurity F, impurity A, impurity C, impurity D, unspecified impurities and total impurities. Other parameters were optical rotation, loss on drying, assay and residual solvent, N,N-dimethyl formamide. Compliance to these specifications was established via batch analysis data and stability studies.

Stability and container closure system

The shelf-life period of Spironolactone API is 60 months when packed in transparent LDPE bags in fiber drums and stored at 30°C in tight containers protected from light.

Quality of the Finished Pharmaceutical Product

Formulation

Spino-25 is a white, round, biconvex film coated tablet packed in ALU/PVC blisters of 10's. 10 blisters are packed in a carton box. Spino-25 contains Spironolactone and other ingredients listed here after: microcrystalline cellulose, maize starch, lactose, povidone, isopropyl alcohol, hydrogenated castor oil powder, colloidal anhydrous silica, croscarmellose sodium, sodium starch glycolate and purified talc. The quantities of all ingredients are confirmed to be in line with the recommendations of Handbook of Pharmaceutical Excipients, Edition 7 in terms of function and quantities. Ingredient, lactose is of safety concern therefore appropriate warnings were included in the product label.

Manufacture

The finished product was manufactured at Brawn Laboratories Limited, 13, New Industrials Township, Industrial Area, Fariadabad-12100, Haryana, India. The compliance of the site to TMDA GMP standards was confirmed through site inspection on April 2018.

Specifications

The FPP is compendia in BP and USP. The manufacturer controls the quality of the finished product as per USP monograph and ICHQ3B requirements. The parameters monitored during quality control are: identification, average weight, dissolution, uniformity of dosage unit, related substances (unknown impurity and total impurity), loss on drying and microbial limit tests. Also assay and residual solvents, isopropyl alcohol and dichloromethane were monitored. Compliance to the standard was established using batch analysis data and stability data.

Stability and container closure system

Stability studies were conducted on three (3) batches of the finished product stored at 30°C ± 2°C, relative humidity 75 % ± 5 % for 24 months and 40°C ± 2°C, relative humidity 75 % ± 5 % for 6 months. Based on the stability data presented, the approved shelf-life is 24 months when stored in ALU/PVC blisters at below 30°C and protected from light and moisture.

Safety and efficacy information

Safety and efficacy of Spino-25 was established through bioequivalence trial.

Study title	A balanced, open label, analyst blind, single centre, two treatment, two period, two sequence, bioequivalence study of spironolactone tablets USP 25 mg of Brawn Laboratories Limited, India with Aldactone (Spironolactone tablets 25 mg) of Pfizer Limited, United Kingdom in 26 health, adult, male, human subject under fed condition in a randomized, crossover design.	
Study design	A balanced, open label, analyst blind, single centre, two treatment, two period, two sequence, bioequivalence study in healthy, adult, male, human subjects under fed conditions in a randomized, crossover design	
Study site	Huclin Research Limited, No 4 Ticel Bio Park, Tharamani, Chennai – 600113	
Study dates	22/01/2016 – 31/01/2016	
Primary objective	To assess the oral bioequivalence of Spironolactone tablets of Brawn Laboratories Limited, India with Aldactone 25 mg of Pfizer Limited, United Kingdom	
Secondary objective	To monitor the safety and tolerability of the test product as compared to the reference product in healthy subjects.	
Number of participants	26 subjects were enrolled and 24 subjects completed the clinical phase of the study	
Monitored parameters	Tmax, half-life, AUC extrapolated, Cmax	
Investigational medicinal products	Test Product	Reference product
	Brand name: Spino-25 Strength: 25 mg Batch number: BT1115032	Brand name: Aldactone Strength: 25 Batch number: 22417

	Expiry date: 10/2017 MAH: Brawn Laboratories Limited	Expiry date: 02/2017 MAH: Pfizer Limited, UK
Analytical method	A validated LC-MS/MS method was used	
Statistical method	ANOVA and 90% confidence intervals were performed using SAS^R Software (Version 9.2)	

Efficacy results are summarized as follows:

Parameter	**Test**	**Reference**	**% Ratio of geometric means**	**90 % Confidence interval**	**DF**	**CV (%)**
AUC0-t (ng*hr/mL)	112.8127	109.9971	102.90	95.86 – 110.45	22	14.36%
AUC0-inf (ng*hr/mL)	115.8539	112.8692	102.56	96.24 – 109.29	22	12.88%
Cmax (ng/mL)	26.8990	26.1413	102.64	96.54 – 109.13	22	12.42%

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, <Spino-25> is equivalent and interchangeable with <Aldactone> 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. <Spino-25> is recommended for registration.

5. Post-approval updates

Variation applications

Reference number	Date submitted	Change requested	Recommendation	Granting date
Nil	-	-	-	-

Feedback from pharmacovigilance, post marketing surveillance and enforcement activities

Type of feedback	Impact	Response
-	-	-

Re-registration applications

NA

PART 5: CHANGE HISTORY

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

Annex I: Mock up label