TANZANIA MEDICINES AND MEDICAL DEVICES AUTHORITY

PUBLIC ASSESSMENT REPORT FOR CO-ANGINET 160/25 (VALSARTAN 160 MG/HYDROCHLOROTHIAZIDE 25 MG) FILM COATED TABLETS

Version number 1.0
10 April, 2022

P. O. Box 77150, EPI Mabibo, Off Mandela Road, Dar es Salaam, Tanzania
Tel: +255-22-2450512/2450751/ 2452108; Fax: +255-22-2450793
Email: info@tmda.go.tz; Website: mwww.tmda.go.tz

1. Introduction

Co-Anginet® 160/25 is a generic medicine of CoDiovan forte 160 mg/25 mg tablets, Novartis Pharma GmbH. Fixed combination antihypertensive agents i.e. valsartan, an angiotensin receptor blocker (ARB), and hydrochlorothiazide, a thiazide diuretic. Hydrochlorothiazide is a diuretic that produces smooth muscle cell relaxation and volume depletion. Hypokalaemia is a known side effect of thiazide diuretic therapy. The addition of an ARB to a thiazide diuretic has a potentially synergistic effect on blood pressure reduction by blocking the actions of angiotensin II at the AT1 receptor and also attenuates diuretic-induced hypokalaemia. Co-Anginet® is approved in Tanzania for use only in adult patients.

1.1 Product details

Registration number	TAN 22 HM 0145
Brand name	Co-Anginet® 160/25
Generic name, strength, and form	Each film-coated tablet contains Valsartan 160 mg and Hydrochlorothiazide 25 mg
ATC classification	ATC Code- C09DA03 - Angiotensin II antagonists and diuretics combinations
Distribution category	POM
Country of origin	Jordan
Associated product	Co-Anginet®80/12.5, Co-Anginet®160/12.5
Marketing Authorization Holder	United Pharmaceuticals Manufacturing Company Limited, Al Rageem Sahab, Amman-Jordan E-mail: samar.amaireh@mspharma.com
Local Technical Representative	Wide Spectrum(Tanzania) limited Sikukuu Str, Kariakoo, P.O BOX 90518 Dar-es-Salaam, Tanzania E-mail:widespectrumtz@yahoo.com

1.2 Assessment procedure

The application for registration of Co-Anginet® 160/25 was submitted on 05 July 2017. The product underwent full assessment. Assessment was completed in 3 (three) rounds of evaluation and the product was registered on 11th April, 2022.

1.3 Information for users

Visual description of the finished product	Light brown caplet biconvex film coated tablets with T17 on one side and plain on the other side
Primary packing material	Alu/Alu Blister
Secondary packing materials	A printed carton box
Shelf-life and storage condition	36 months, Store up to 30ºC
Route of administration	Oral
Therapeutic indications	Treatment of essential hypertension in adults.

	Valsartan/hydrochlorothiazide fixed-dose combination is indicated in patients whose blood pressure is not adequately controlled on valsartan or hydrochlorothiazide monotherapy.

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: Co-Anginet® 160/25

Composition: Each film-coated tablet contains Valsartan 160 mg and Hydrochlorothiazide 25 mg

Pack size: 30 film-coated tablets

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

Storage conditions: Store up to 30ºC

Manufacturer address: physical address of release site

Unique identifier: Not applicable

Special warnings/precautions or instructions for use: See enclosed leaflet

The details of the primary pack include:

Brand name and strength: Co-Anginet® 160/25

Manufacturing details: batch number, manufacturing date and expiry date

Name of manufacturer: United Pharmaceuticals Manufacturing Company 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.

Valsartan

General Information

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

Molecular formula: $C_{24}H_{29}N_5O_3$

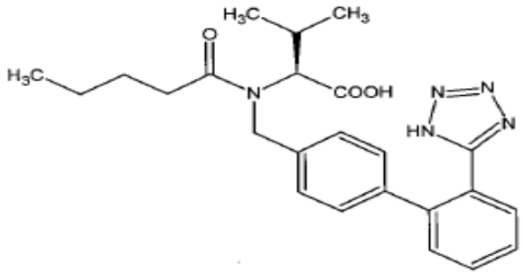
Chemical name:

N-[p-(o-1H-Tetrazol-5-ylphenyl) benzyl]-N-valeryl-L-valine
Or

N-(1-Oxopentyl)-N-[[2′-(1H-tetrazol-5-yl)[1,1′-biphenyl]-4-yl]methyl]-L-valine
Or

(S)-N-(1-carboxy-2-methylprop-1-yl)-N-pentanoyl-N-[2′-(1H-tetrazol-5-yl)-biphenyl-4-ylmethyl] amine

Structure:



General properties

The active substance is white to almost white hygroscopic powder, freely soluble in anhydrous ethanol, sparingly soluble in dichloromethane, practically insoluble in water. The substance shows polymorphism and stereoisomerism. The manufacturer consistently produces the correct isomer and the same polymorphic form.

Valsartan 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

Valsartan API manufacturer is Jubilant Lifesciences Limited, 18,56,57&58 KIADB Industrial Area, Nanjagud 571 302, Mysore, Karnataka, India. The manufacturing complies with GMP requirements as evidenced by the GMP certificate issued by the Drugs Control Administration Government of Karnataka. Valsartan 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, identity (IR and Enantiomeric purity), particle size, enantiomeric purity (Ph. Eur), residual solvent (GC), assay (Ph. Eur), related impurities (Ph. Eur), water content (KF), sulphated ash (Ph. Eur), and nitrosamine impurities (NDEA and NDMA). Compliance to these specifications were established via batch analysis data and stability studies.

Stability and container closure system

The re-test period of Valsartan API is 48 months when packed in double polythene bags followed by aluminium bag and HDPE drum respectively. After packing is complete the metallic ring closing the HDPE drum will be sealed with numbered stainless steel seals with storage condition 'The product should be kept in airtight containers below 25°C'.

Hydrochlorothiazide

General Information

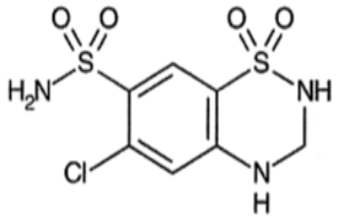
Hydrochlorothiazide API is compendia in USP, Ph.Eur., and BP.

Molecular formula: $C_7H_8ClN_3O_4S_2$

Chemical name:

6-chloro-3, 4-dihydro-2H-1, 2, 4-benzothiazine-7-sulphonsmide-1, 1- dioxide

Structure:



General properties

Hydrochlorothiazide is a white to almost white crystalline powder and is very slightly soluble in water. It has been adequately demonstrated that polymorphic form I is consistently manufactured.

Hydrochlorothiazide is a class II or 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

Hydrochlorothiazide API manufacturer is IPCA Laboratories limited, Sejavta, District Ratlam (Madhya Pradesh) Pin: 457 002, India. The manufacturing complies with GMP requirements as evidenced by the GMP certificate issued by the Food and Drugs administration of Bhopal, India. Hydrochlorothiazide 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: Description, identity (UV, TLC, IR and colour), particle size, chlorides (Ph. Eur), acidity or alkalinity (Ph. Eur), loss on dry (Ph. Eur), residual solvent (GC), assay (Ph. Eur), related impurities (Ph. Eur), and sulphated ash (Ph. Eur). Compliance to these specifications were established via batch analysis data and stability studies.

Stability and container closure system

The re-test period of Hydrochlorothiazide API is 60 months when packed in colorless Poly Bags in HMHDPE Container with storage condition 'Preserve in well closed container'.

Quality of the Finished Pharmaceutical Product

Formulation

Co-Anginet® 160/25 is a light brown caplet biconvex film coated tablets with T17 on one side and plain on the other side.

Co-Anginet® 160/25 contains the Valsartan and Hydrochlorothiazide, and other ingredients listed here after: Microcrystalline cellulose, Cross Povidone, Colloidal silicon dioxide, Magnesium stearate, Yellow iron oxide, Black iron oxide, Red iron oxide. 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 United Pharmaceutical Manufacturing Company Limited, Al-Rageem- Sahab, Amman-Jordan. The compliance of the sites to TMDA GMP standards was confirmed through site inspection on 02 May, 2019.

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 HPLC), average weight, weight variation, hardness, assay, disintegration, dissolution, uniformity of dosage units, 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 'Store up to 30ºC'.

Safety and efficacy information

Safety and efficacy of Co-Anginet® 160/25 was established through a bioequivalence trial.

BE trial report number BC-VAHY-14/396 was submitted.

Study title	Randomized, two- way, two- period, single oral dose, open-label, crossover, bioequivalence study to compare Valsartan/ Hydrochlorothiazide (160/25 mg Valsartan/ Hydrochlorothiazide Tablet) Produced by United Pharmaceuticals Mfg. Co., versus CO-Diovan®(160/25 mg Valsartan/ Hydrochlorothiazide Tablets) Produced by Novartis Pharmaceuticals Corporation Inc., in healthy subjects under fasting conditions
Study design	Open label, randomized, fasting, single dose, two treatment, two-sequence, and two-period crossover study with a washout interval of two weeks between dosing
Study site	ACDIMA BioCenter Amman, Jordan
Study dates	
Primary objective	To assess bioequivalence between a single dose of Valsartan/ Hydrochlorothiazide from products: Valsartan/ Hydrochlorothiazide Tablets ((160/25 mg Valsartan/ Hydrochlorothiazide per Tablet) produced by United Pharmaceuticals Mfg. Co., as a test product, in comparison with CO-Diovan® Tablets (160/25 mg Valsartan/ Hydrochlorothiazide per Tablets) produced by Novartis Pharmaceuticals Corporation Inc., Italy, as a reference product in terms and extent of absorption applying two-by-two crossover design in healthy subjects under fasting conditions
Secondary objective	To monitor the adverse events and to ensure the safety of the subjects
Number of participants	Planned: 36 subjects Enrolled: 36 subjects

	Dosed: 36 subjects Withdrawn – 04 subjects Completed: 32 subjects, Bio-sample analyzed: 32 subjects Pharmacokinetic and statistical data analyzed: 32 subjects	
Monitored parameters	Tmax, Cmax, AUC0→t, AUC0→∞, AUC% Extrapolation Kel and T1/2	
Investigational medicinal products	Test Product	Reference product
	Strength: 25 mg Batch number: 2012170 Expiry date: 07/2018	Strength: 25 mg Batch number: 008477 Expiry date: 06/2018
Analytical method	LC-MS/MS method was used for the determination of plasma concentration of analytes	
Statistical method	*WinNonlin Professional Software*	

Efficacy results are summarized as follows:

For Vasartan

Pharmacokinetic Results of Valsartan

Parameter	Test Product (Mean ± SD)	Reference Product (Mean ± SD)
C_{max} (ng/ml)	3561.52±2084.05	3391.65±2016.01
AUC_{0-t} (ng × hr/ml)	22977.13±12908.76	21972.99±11281.16
$AUC_{0-\infty}$ (ng × hr/ml)	23577.83±13029.60	22602.02±11381.18
T_{max} (hr)	2.833±1.113	2.853±1.141
T_{half} (hr)	7.508±1.270	7.859±1.558
$K_{elimination}$ (hr^{-1})	0.09480±0.01557	0.09135±0.01670

Valsartan % Point Estimate & Confidence Interval (Kinetica Output)

Parameter	Point Estimate	Lower Limit	Upper Limit
C_{max}	102.81	85.72	123.30
AUC_{0-t}	101.05	89.40	114.22
$AUC_{0-\infty}$	100.97	89.92	113.37

Valsartan % Point Estimate & Confidence Interval (SAS Output)

Parameter	Point Estimate	Lower Limit	Upper Limit
C_{max}	102.81	85.72	123.29
AUC_{0-t}	101.05	89.40	114.21
$AUC_{0-\infty}$	100.97	89.92	113.37

For Hydrochlorothiazide

Pharmacokinetic Results of Hydrochlorothiazide

Parameter	Test Product (Mean ± SD)	Reference Product (Mean ± SD)
C_{max} (ng/ml)	155.219±63.373	145.619±41.148
AUC_{0-t} (ng × hr/ml)	1062.85±332.94	986.54±277.28
$AUC_{0-\infty}$ (ng × hr/ml)	1088.99±337.49	1016.81±272.97
T_{max} (hr)	2.229±0.778	2.417±1.062
T_{half} (hr)	9.509±0.684	9.690±0.806
$K_{elimination}$ (hr^{-1})	0.07327±0.00550	0.07207±0.00673

Hydrochlorothiazide % Point Estimate & Confidence Interval (Kinetica Output)

Parameter	Point Estimate	Lower Limit	Upper Limit
C_{max}	103.47	94.74	112.99
AUC_{0-t}	106.69	101.49	112.15
$AUC_{0-\infty}$	105.79	100.78	111.05

Hydrochlorothiazide % Point Estimate & Confidence Interval (SAS Output)

Parameter	Point Estimate	Lower Limit	Upper Limit
C_{max}	103.47	94.74	112.99
AUC_{0-t}	106.69	101.49	112.15
$AUC_{0-\infty}$	105.79	100.78	111.04

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, Co-Anginet® 160/25 (160/25 mg Valsartan/ Hydrochlorothiazide) tablets produced by United Pharmaceuticals Mfg. Co. is equivalent and interchangeable with CO-Diovan® (160/25 mg Valsartan/ Hydrochlorothiazide) tablets produced by Novartis Pharmaceuticals Corporation Inc. 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. Co-Anginet® 160/25 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

NA

PART 5: CHANGE HISTORY

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

Annex I: Mock up labels;

Primary pack label;

CO-ANGINET® 160/25 mg
Valsartan / Hydrochlorothiazide
123 mm

Secondary pack label;