THEUNITEDREPUBLICOFTANZANIA

MINISTRYOFHEALTH

TANZANIA MEDICINES AND MEDICAL DEVICES AUTHORITY

PUBLIC ASSESSMENT REPORT FOR VIVAZAC PLUS (IRBESARTAN AND HYDROCHLOROTHIAZIDE 300MG/25MG, 300MG/12.5MG,150MG/12.5) TABLETS

Version number 1.0
11th October 2023

TMDA Headquarters, Plot No. 56/1, Block E, Kisasa B Centre, Hombolo Road, P. O. Box 1253, Dodoma - Tanzania,
Tel: +255 (26) 2961989/2061990/ +255(22) 2450512/2450751/2452108,
Email: info@tmda.go.tz, Website: www.tmda.go.tz, Toll free: 08001100834

1. Introduction

Vivazac Plus Tablets is a generic medicine of Irbesartan / Hydrochlorothiazide tablets. Vivazac Plus is an antihypertensive medicine belonging to C09DA04- angiotensin-II antagonists, combination group. Vivazac® Plus exerts its activity by an additive antihypertensive effect, reducing blood pressure to a greater degree than either component alone. Vivazac® Plus is approved in Tanzania for use in adults.

1.1 Product details

Registration number	Vivazac Plus 300/25: TAN 20 HM 0353 Vivazac Plus 30/12.5: TAN 20 HM 0347 Vivazac Plus 150/12.5: TAN 20 HM 0351
Brand name	Vivazac Plus 300/25 Vivazac Plus 300/12.5 Vivazac Plus 150/12.5
Generic name, strength and form	Irbesartan 300 mg / Hydrochlorothiazide 25mg tablets Irbesartan 300 mg / Hydrochlorothiazide 12.5mg tablets Irbesartan 150 mg / Hydrochlorothiazide 12.5mg tablets
ATC classification	C09DA04- angiotensin-II antagonists, combination
Distribution category	POM
Country of origin	Jordan
Associated product	NA
Marketing Authorization Holder	United Pharmaceuticals Manufacturing Limited Company, Al-Rageem- Sahab Amman**-Jordan** E-Mail: samar.amaireh@mspharma.com
Local Technical Representative	Wide Spectrum (T) Limited, Sukuku Street Kariakoo, P.O. Box: 90518, Dar Es Salaam**-Tanzania**

1.2 Assessment procedure

The application for registration of Vivazac Plus was submitted on 05/05/2017. The product underwent full assessment. Assessment was completed in 4 rounds of evaluation. Vivazac Plus was registered on 25/09/2020.

1.3 Information for users

Visual description of the finished product	Vivazac Plus 300/25: Brick red colour biconvex caplet shape tablet embossed with E43 on one side and plain on the other

	Vivazac Plus 300/12.5: Peach, biconvex caplet shape tablet, embossed with U7I on one side and plain on the other Vivazac Plus 150/12.5: Light pink colour caplet shape tablet scored on one side and plain on the other
Primary packing material	PVC/PVDC/Alu
Secondary packing materials	
Shelf-life and storage condition	24 months Store up to 30°C, protect from moisture
Route of administration	Oral
Therapeutic indications	VIVAZAC® PLUS is indicated for the treatment of high blood pressure (essential hypertension), when treatment with Irbesartan or Hydrochlorothiazide alone did not provide adequate control of blood pressure

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 <full prescribing information as per SmPC/both full prescribing information as per SmPC and simplified information for patients/simplified information for patients>.

Container labels

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

Brand name: Vivazac Plus 300/25, Vivazac Plus 300/12.5,Vivazac Plus 150/12.5

Composition:300 mg Irbesartan / 25mg Hydrochlorothiazide, 300 mg Irbesartan / 12.5mg Hydrochlorothiazide, 150 mg Irbesartan /12.5mg Hydrochlorothiazide

Pack size: 3 × 10 tablets

Manufacturing details: batch number, manufacturing date, expiry date

Storage conditions: Store up to 30°C, protect from moisture.

Manufacturer address: United Pharmaceuticals Manufacturing Limited Company, Al-Rageem-Sahab, Amman-Jordan

Unique identifier: <state the unique identification used>

Special warnings/precautions or instructions for use: The product contains lactose

The details of the primary pack include:

Brand name and strength: Vivazac Plus 300/25, Vivazac Plus 300/12.5,Vivazac Plus 150/12.5
Manufacturing details: <batch number, manufacturing date, expiry date>
Name of manufacturer: United Pharmaceuticals

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.

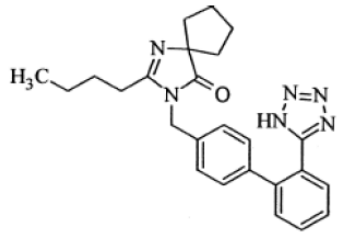
3. Scientific discussion

Quality of Active Pharmaceutical Ingredient(s)

Irbesartan

Information on quality of the API was submitted in form of APIMF.

General properties
Irbesartan API is compendia in BP.
Molecular formula: $C_{25}H_{28}N_6O$
Chemical name: 1,3-Diazaspiro[4.4]non-1-en-4-one,2-butyl-3-[[2'-(1H-tetrazol-5-yl)[1,1'- biphenyl]-4-yl]-methyl]-
Structure:



Critical physico-chemical properties of the API were sparingly soluble in Methanol, slightly soluble in Methylene Chloride and practically insoluble in Water.It exhibits polymorphism and form-A is manufactured.

Manufacture
The API manufacturing site, Jubilant Generics Limited/ #18,56,57 & 58, K.I.A.D.B Industrial area, Nanjangud, Mysore District 571 302 Karnataka, India was noted to comply with WHO GMP requirements as evidenced by the GMP certificate issued by Government of Karnataka Drugs Control Department. Irbesartan 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.Eur standards and ICHQ3A. The parameters monitored during quality control are: characters,solubility, identification , appearance of solution, water content, heavy metals, sulphated ash, limit of azide (trinitride): N3- (Impurity B), related substances,assay, residual sovents,particle size, content of NDMA impurity and content of NDEA impurity .Compliance to these specifications were established via batch analysis data and stability studies.

Stability and container closure system

The re-test period of Irbesartan API is 48 months when packed in polyethylene bag and stored at below 25°C.

Hydrochlorothiazide

Information on quality of the API was submitted in form of CEP.

General properties

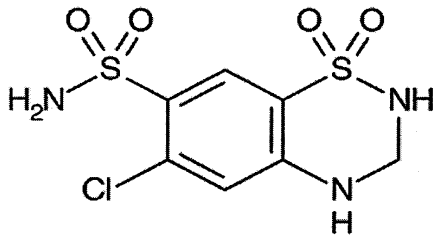
Hydrochlorothiazide API is compendia in BP/Ph.Eur.

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:

STRUCTURE



Critical physico-chemical properties of the API were very slightly soluble in water, soluble in acetone, sparingly soluble in Ethanol (96%).It exhibits polymorphism and form-I is consistenly manufactured.

Manufacture

The API manufacturing site, IPCA Laboratories limited// Sejavta, District Ratlam (Madhya Pradesh) Pin: 457 002 , India was noted to comply with WHO GMP requirements as evidenced by the GMP certificate issued by <state the issuing authority>. 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 Ph.Eur standards and ICHQ3A. The parameters monitored during quality control are: description, identification, chlorides, acidity or alkalinity, loss on drying, sulphated ash, related substances,assay, residual solvents,formaldehyde content, polymorphic test and particle size .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 LDPE bag and stored at below 30°C.

Quality of the Finished Pharmaceutical Product

Formulation

Vivazac Plus 300/25: Brick red colour biconvex caplet shape tablet embossed with E43 on one side and plain on the other

Vivazac Plus 300/25 is a brick red colour biconvex caplet shape tablet embossed with E43 on one side and plain on the other.

Vivazac Plus 300/12.5 is a peach, biconvex caplet shape tablet, embossed with U7I on one side and plain on the other

Vivazac Plus 150/12.5 is a light pink colour caplet shape tablet scored on one side and plain on the other.

Vivazac Plus contains Irbesartan and Hydrochlorothiazide and other ingredients listed hereafter lactose monohydrate, croscarmellose sodium, starch, hypromellose, microcrystalline cellulose colloidal silicon dioxide, magnesium stearate, HPMC based coating system (opadry white oy-l-28900), yellow iron oxide, red iron oxide. The quantities of all ingredients are confirmed to be in line with the recommendations of Handbook of Pharmaceutical Excipients, Edition 8th 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 United Pharmaceuticals Manufacturing Limited Company, Al-Rageem- Sahab, Amman-Jordan. The compliance of the site to TMDA GMP standards was confirmed through site inspection on 3rd & 4th October, 2018.

Specifications

The FPP is compendial in USP. The manufacturer controls the quality of the finished product as per USP and ICHQ3B requirements. The parameters monitored during quality control are:

description, identification, average weight, weight variation, uniformity of dosage units, disintegration, dissolution, related substances, assay and microbial limit test. Compliance to the standard was established using batch analysis data and stability data.

Stability and container closure system

Stability studies were conducted on 3 batches of the finished product stored at 30°C ± 2°C, 65 % ± 5 % for 24 months and 40°C ± 2°C, 75 % ± 5 % for 6 months. Based on the stability data presented, the approved shelf-life is 24 months when stored in PVC/PVDC/Al blisters at below 30ºC.

Safety and efficacy information

Vivazac Plus 300/25

Safety and efficacy of Vivazac Plus 300/25 was established through bioequivalence trial.BE trial report number <number> was submitted.

In case of BE:

Study title	Bioequivalence study of Irbesartan & Hydrochlorothiazide Tablets (300 mg Irbesartan/25 mg Hydrochlorothiazide) I United Pharmaceuticals Mfg. CO., versus Co Aprovel® Tablets (300 mg Irbesartan/25 mg Hydrochlorothiazide) I Sanofi Winthrop Industrie, fo llowing a single dose administration to healthy adults under fasting condition	
Study design	An open label, randomized, fasting, single dose, two-treatment, two-sequence, and two period crossover, laboratory-blind study with a washout interval of one week between dosing	
Study site		
Study dates	06/05/2011 – 15/06/2011 (clinical and bioanalytical phases)	
Primary objective	To compare the pharmacokinetic behaviors of Irbesartan/ Hydrochlorothiazide and Co Aprovel ® in vivo to conclude if Irbesartan is bioequivalent to Co Aprovel ® under fasting conditions	
Secondary objective		
Number of participants	28	
Monitored parameters	Cmax, AUCt and AUCinf	
Investigational medicinal products	Test Product Irbesartan & Hydrochlorothiazide Tablets of	Reference product Co Aprovel® Tablets of Sanofi Winthrop Industrie,France

	United Pharmaceuticals Mfg. CO.	
	Strength:300 mg Irbesartan/25 mg Hydrochlorothiazide Batch number: 7940 Expiry date: 12/2012	Strength:300 mg Irbesartan/25 mg Hydrochlorothiazide Batch number: 358 Expiry date: 01/2013
Analytical method		
Statistical method	Kinetica software/version 5.0 and Microsoft excel	

Efficacy results are summarized as follows:

Irbesartan

Parameter	Test	Reference	% Ratio of geometric means	90 % Confidence interval	DF	CV (%)
AUC0-t (ng*hr/ml)			102.63			
AUC0-inf (ng*hr/ml)			102.14			
Cmax (ng/ml)			108.71			

Hydrochlorothiazide

Parameter	Test	Reference	% Ratio of geometric means	90 % Confidence interval	DF	CV (%)
AUC0-t (ng*hr/ml)			94.49			
AUC0-inf (ng*hr/ml)			95.31			
Cmax (ng/ml)			90.61			

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, Vivazac Plus 300/25 is equivalent and interchangeable with Co Aprovel® Tablets under acceptable in vivo experimental conditions.

Vivazac Plus 300/12.5

Safety and efficacy of Vivazac Plus 300/12.5 was established through biowaiver application. Comparative dissolution report number <number> was submitted.

In case of biowaiver
The biowaiver was approved based on additional strength.

Vivazac Plus 300/12.5 fulfilled the criteriafor waiving an in-vivo bioequivalence study as per relevant TMDA guidance. Dissolution profiles of Vivazac Plus 300/12.5 was compared to Vivazac Plus 300/25 . Less than 85% of the labelled amount of Irbesartan and at least 85% of the labelled amount of Hydrochlorothiazide had dissolved in all three media. Therefore, necessitating calculation of similarity factor f2, which was noted to be above 50.

Vivazac Plus 150/12.5
Safety and efficacy of Vivazac Plus 150/12.5 was established through biowaiver application/clinical trial. Comparative dissolution report number <number> was submitted.

The biowaiver was approved based on additional strength.

Vivazac Plus 150/12.5 fulfilled the criteriafor waiving an in-vivo bioequivalence study as per relevant TMDA guidance. Dissolution profiles of Vivazac Plus 150/12.5 was compared to Vivazac Plus 300/25 . Less than 85% of the labelled amount of Irbesartan and at least 85% of the labelled amount of Hydrochlorothiazide had dissolved in all three media. Therefore, necessitating calculation of similarity factor f2, which was noted to be above 50.

4. Benefit-Risk Assessment and Conclusion

On basis ofthe 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. Vivazac Plus 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 label

Vivazac Plus 300/25

90 mm

Vivazac Plus 300/12.5


Vazac® Plus
Irbesartan / Hydrochlorothiazide
300/12.5 mg
United Pharmaceuticals
M3-10-0539

Vivazac Plus 150/12.5


Vazac® Plus
Irbesartan / Hydrochlorothiazide
150/12.5 mg
United Pharmaceuticals
M3-10-0428

Effective date: 03/10/2022