TMDA/DMC/MRE/F/016
Version#1

TANZANIA MEDICINES AND MEDICAL DEVICES AUTHORITY

PUBLIC ASSESSMENT REPORT FOR CDTEL-H® (TERMISATARTAN 40 MG AND HYDROCHLOROTHIAZIDE 12.5 MG) TABLETS

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1. Introduction

CDTEL-H (40 mg telmisartan/12.5 mg hydrochlorothiazide) is a generic medicine of innovator product Micardis Plus 40 mg/12.5 mg marketed by Boehringer Ingelheim, Germany. CDTEL-H is a fixed dose combination of the active substance Telmisartan and Hydrochlorothiazide, an angiotensin II antagonists and diuretics medicine belonging to ATC code C09DA07.

Telmisartan is an active angiotensin II receptor antagonist. Angiotensin II has an important role in the renin-angiotensin system by stimulation of the sympathetic activity, arteriolar vasoconstriction and water and salt retention. These effects result in an increase in blood pressure. Treatment with an angiotensin type 2 antagonist blocks this action and is therefore indicated for essential hypertension and renal disease in patients with hypertension and type 2 diabetes mellitus as part of an antihypertensive medical product regimen.

Hydrochlorothiazide is a thiazide diuretic. It affects electrolyte reabsorption mechanisms in the kidney, by inhibition of the Na+ Cl- symporter. The increased sodium and chloride excretion will result in a decreased plasma volume. The resulting plasma renin activity, aldosterone secretion and urinary potassium excretion is partially mediated by angiotensin II.

CDTEL-H (Telmisartan 40.00 mg and Hydrochlorothiazide 12.50 mg) is approved in Tanzania for treatment of essential hypertension in adults.

1.1 Product details

Registration number	TAN 21 HM 0103
Brand name	CDTEL-H
Generic name, strength and form	Telmisartan USP 40.00 mg and Hydrochlorothiazide USP 12.50 mg Tablets
ATC classification	C09DA07; Telmisartan and diuretics
Distribution category	POM
Country of origin	India
Associated product	Nil
Marketing Authorization Holder	Zota Healthcare Limited, "ZOTA HOUSE", 2/896, Hira Modi Street, Sagrampura, Surat-395 002 (Gujarat), India.
Local Technical Representative	Moraf Pharmaceuticals Limited, Kipande Street, Kariakoo, P. O. Box 21323, Dar Es Salaam, Tanzania.

1.2 Assessment procedure

The application for registration of CDTEL-H was submitted on 22/03/2017. The product underwent full assessment. Assessment was completed in three (3) rounds of evaluation. CDTEL-H was registered on 29/03/2021.

1.3 Information for users

Visual description of the finished product	White, convex, round shaped uncoated tablets
Primary packing material	Alu- Alu blister strip/blister of 10 tablets
Secondary packing materials	3 strips/blisters are packed in a printed carton
Shelf-life and storage condition	36 months. Do not store above 30°C
Route of administration	Oral
Therapeutic indications	Treatment of essential hypertension in adults

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.

Container labels
The product label information is presented in English. Details in the secondary pack label include:
Brand name: CDTEL-H
Composition: Telmisartan USP 40.00 mg and Hydrochlorothiazide USP 12.50 mg
Pack size: 3 Strips each of 10 tablets
Manufacturing details: batch number, manufacturing date, expiry date are indicated.
Storage conditions: Store below 30^0C, Protected from moisture
Manufacturer address: Zota Healthcare Limited located at Plot No. 169, Surat Special Economic Zone, Nr. Sachin Railway Station, Surat-394230, (Gujarat), India
Unique identifier: NA
Special warnings/precautions or instructions for use: CDTEL-H contains lactose

The details of the primary pack include:
Brand name and strength: CDTEL-H (Telmisartan 40.00 mg and Hydrochlorothiazide 12.50 mg)
Manufacturing details: batch number, manufacturing date and expiry date are indicated
Name of manufacturer: is indicated

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 currently not available.

3. Scientific discussion

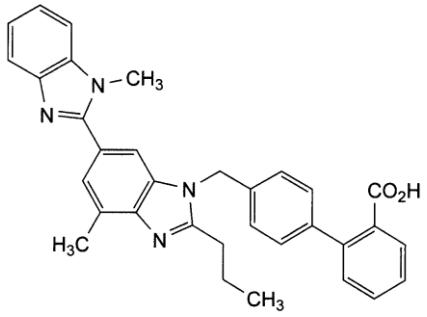
Quality of Active Pharmaceutical Ingredient(s) (APIs)

The active substances are telmisartan and hydrochlorothiazide. Information on quality of the API was submitted in form of full details of the product dossier.

Telmisartan and hydrochlorothiazide APIs are well established that are both described in the United States Pharmacopoeia and British Pharmacopoeia.

General Information

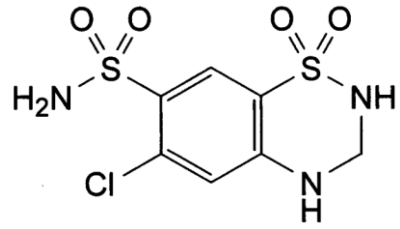
Telmisartan;
Molecular formula: $C_{33}H_{30}N_4O_2$
Chemical name: 4′-[[4-Methyl-6-(1-methyl-1H-benzimidazol-2-yl)-2-propyl-1H-benzimidazol-1-yl]methyl][1,1′-biphenyl]-2-carboxylic acid
Structure:



Hydrochlorothiazide;
Molecular formula: $C_7H_8ClN_3O_4S_2$

Chemical name: 6-Chloro-3,4-dihydro-2H-1,2,4-benzothiadiazine-7-sulphonamide 1,1-dioxide

Structure:



General properties

Telmisartan is a white or slightly yellowish crystalline powder, which practically is insoluble in water, slightly soluble in methanol, sparingly soluble in methylene chloride. It dissolves in 1 M sodium hydroxide. It exhibits polymorphism. Differential scanning calorimetry and X-Ray Powder Diffraction studies confirm that the manufacturing process used consistently produces the same polymorphic form.

Hydrochlorothiazide is a white or almost white, crystalline powder, which is slightly soluble in water; freely soluble in sodium hydroxide solution, in n-butylamine, and in dimethylformamide sparingly soluble in methanol, in soluble in ether, in chloroform, and in dilute mineral acids. It exhibits polymorphism. The manufacturing process consistently produces the same polymorphic form.

Therefore, critical physico-chemical properties of the APIs that can affect the performance of the drug product are solubility, particle size, polymorphism.

Telmisartan

Manufacture

Telmisartan API manufacturer is Sequel Pharmaceuticals (India) Pvt. Limited located at N/46, additional MIDC, Anand Nagar, Ambernath, Maharashtra-India. The manufacturing complies with GMP requirements as evidenced by the GMP certificate issued by Office of Joint Commissioner, Food and Drug Administration, Maharashtra state, India. Telmisartan 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 ICH requirements. The parameters monitored during quality control are: description, solubility, identification (by IR and HPLC), residue on ignition, heavy metals, related substances, loss on drying, assay, residual solvents, polymorphism and particle size distribution. Compliance to these specifications were established via batch analysis data and stability studies.

Stability and container closure system
The shelf-life of Telmisartan API is 36 months when packed in polythene bag and stored at or below 25^0C.

Hydrochlorothiazide

Manufacture

Hydrochlorothiazide API manufacturer is CTX Life Sciences Pvt. Limited located at Block No. 251-252, Sachin Magdalla Road, G.I.D.C, Sachin, Surat - 394230, Gujarat, India. The manufacturing complies with GMP requirements as evidenced by the GMP certificate issued by Food and Drug Control Administration, Gujarat State, 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 USP standards and ICH requirements. The parameters monitored during quality control are: description, solubility, identification (by IR and UV), residue on ignition, heavy metals, related substances, loss on drying, Chloride, Selenium and assay. Compliance to these specifications were established via batch analysis data and stability studies.

Stability and container closure system
The shelf-life of Hydrochlorothiazide API is 60 months when packed in clear LDPE bag and stored at or below 30^0C.

Quality of the Finished Pharmaceutical Product

Formulation

CDTEL-H is a white, convex, round shaped uncoated tablets. It contains the APIs **T**elmisartan and hydrochlorothiazide.

The excipients are: Microcrystalline cellulose, Lactose, Colloidal Silicon Dioxide, Magnesium Hydroxide, Crospovidone, Polyvinyl Pyrrolidone (PVPK 30), Colloidal Silicon Dioxide, Magnesium Stearate and Purified Talc.

The quantities of all ingredients are confirmed to be in line with the recommendations of Handbook of Pharmaceutical Excipients, 7th Edition in terms of function and quantities. The formulation contains Lactose which is of safety concern therefore appropriate warnings are included in the product label and summary of product characteristics (SmPC).

The tablets are packed in aluminium/aluminium blister packs of 10 tablets.

Manufacture

The finished product manufacturer is Zota Healthcare Limited located at Plot No. 169, Surat Special Economic Zone, Nr. Sachin Railway Station, Surat-394230, (Gujarat), India. The manufacturing site complies with TMDA cGMP standards.

Specifications

The FPP is compendia in USP. The manufacturer controls the quality of the finished product as per USP, inhouse specifications (for test of average weight, uniformity of weight and uniformity of dosage unit) and ICHQ requirements. The parameters monitored during quality control are: Description, Identification (HPLC and UV), Average weight of tablet, Uniformity of weight, Disintegration Time, Dissolution, Uniformity of dosage unit, 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 (three) batches of the finished product stored at 30 ± 2°C & RH: 65 ± 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 strip of 10 tablets at or below 30◦C.

Safety and efficacy information

Safety and efficacy of CDTEL-H was established through bioequivalence trial. BE trial report number BE-45-2017 was submitted.

Study title	A randomized, Open label, balanced, two treatment, two Period, two sequence, single dose, crossover, bioequivalence study of CDTEL-H (Telmisartan 40 mg and Hydrochlorothiazide 12.5 mg) of Zota Healthcare Ltd, India with Micardis Plus (Telmisartan 40 mg and Hydrochlorothiazide 12.5 mg) of Boehringer Ingelheim, Germany in Normal, Healthy, adult human subject under fasting condition
Study design	A randomized, open label, balanced, two treatment, two Period, two sequence, single dose, crossover, bioequivalence study
Study site	**Clinical study and Bio-analytical study site;** Azidus Laboratory Limited,

	No. 23rd School Road, Rathinamangalam, Behind Tagore Engineering College (Via) Vandalur, Kelambakkam Road, Chennai, Tamil Nadu, India.	
Study dates	Period I (dosing); 02-08-2017 Period II (dosing); 07-08-2017	
Primary objective	To compare the bioequivalence and characterize the pharmacokinetic profile of the sponsor's CDTEL-H relative to that of reference product Micardis Plus of Boehring Ingelheim Germany in healthy, adult, human male subjects under fasting conditions and to assess the bioequivalence	
Secondary objective	To monitor the safety of the subjects	
Number of participants	24 Subjects	
Monitored parameters	The pharmacokinetic parameters determined were Cmax, Tmax, AUC_{0-32}, $AUC_{0-\infty}$ and T½, which were measured and calculated from the collected blood samples for telmisartan and hydrochlorothiazide	
Investigational medicinal products	Test Product	Reference product
	Strength: Telmisartan 40 mg and Hydrochlorothiazide 12.5 mg Batch number: LN27002 Expiry date: Aug, 2019	Strength: Telmisartan 40 mg and Hydrochlorothiazide 12.5 mg Batch number: 506748A Expiry date: Aug, 2018
Analytical method	LC-MS/MS methods were used for the determination of plasma concentrations of both analytes The analytical range for telmisartan was 1.09 – 601.86 ng/ml in the biostudy For hydrochlorothiazide the calibration curve ranged from 0.809 – 350.03ng/ml in the biostudy	
Statistical method	The statistical analysis was carried out according to the bioequivalence guideline	

Efficacy results are summarized as follows:

For Telmisartan;

Parameter	**Test**	**Reference**	**% Ratio of geometric means**	**90 % Confidence interval**	**DF**
AUC0-32 (ng.h/ml)	2767.58	2938.46	95.43	80.98-124.90	47
AUC0-inf (ng.h/ml)	2946.50	3099.71	95.60	81.30-107.48	47
Cmax (ng/ml)	488.23	508.22	96.56	85.58-108.76	47

For Hydrochlorothiazide;

Parameter	Test	Reference	% Ratio of geometric means	90 % Confidence interval	DF
AUC0-32 (ng.h/ml)	513.17	489.92	105.25	92.49-124.45	47
AUC0-inf (ng.h/ml)	515.13	506.33	102	81.79-120.67	47
Cmax (ng/ml)	85.7	86.7	99.42	80.16-122.09	47

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, CDTEL-H was considered bioequivalent and interchangeable with Micardis Plus 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. CDTEL-H is recommended for registration.

5. Post-approval updates

Variation applications

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

Feedback from pharmacovigilance, post marketing surveillance and enforcement activities

Type of feedback	Impact	Response
Nil	Nil	Nil

Re-registration applications

NA

PART 5: CHANGE HISTORY

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