TANZANIA MEDICINES AND MEDICAL DEVICES AUTHORITY

PUBLIC ASSESSMENT REPORT FOR TENGLYN 20 MG (TENELIGLIPTIN HEMIPENTAHYDROBROMIDE HYDRATE EQUIVALENT TO TENELIGLIPTIN 20 MG) FILM COATED TABLETS

Version number 1.0
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1. Introduction

Tenglyn 20mg is a generic medicine of Tenelia 20mg Tablets manufactured by Mitsubishi Tanabe Pharma Corporation & Daiichi Sankyo, Japan. The proposed product is a tablet that contains, as the active ingredient, teneligliptin hemipentahydrobromide hydrate (hereinafter referred to as teneligliptin), a dipeptidyl peptidase (DPP)-4 inhibitor. DPP-4 inhibitors are therapeutic drugs for type 2 diabetes that increase the concentration of active glucagon-like peptide-1 (GLP-1) in the blood, thus promoting glucose-dependent insulin secretion, and inhibiting glucagon secretion, resulting in antihyperglycemic effects. Tenglyn 20mg is approved in Tanzania for use in adult patients.

1.1 Product details

Registration number	TAN 21 HM 0210
Brand name	Tenglyn 20mg
Generic name, strength, and form	Each film coated tablet contains: Teneligliptin Hemipenta Hydrobromide Hydrate equivalent to Teneligliptin 20 mg
ATC classification	Dipeptidyl peptidase 4 (DPP4) inhibitors (Antidiabetic) ATC code: A10BH
Distribution category	POM
Country of origin	India
Associated product	N/A
Marketing Authorization Holder	Cadila Healthcare Limited, Zydus Tower, Satellite Cross Roads, Ahmedabad 380 015, India Email: rajeev.nanda@zyduscadila.com
Local Technical Representative	Abacus Pharma (A) Ltd, 18C, Warehouse No. 4, Nyerere Road, P.O. Box 12294, Dar es salaam, Tanzania Email: rakeshu@kibokogroup.com

1.2 Assessment procedure

The application for registration of Tenglyn 20mg was submitted on 26 June 2018. The product underwent full assessment. Assessment was completed in 2 (two) rounds of evaluation and the product was registered on 03 June 2021.

1.3 Information for users

Visual description of the finished product	Light pink colored, round shaped, biconvex, film coated tablets, plain on both sides
Primary packing material	PVC/Alu blisters
Secondary packing materials	A printed carton box
Shelf-life and storage condition	24 months, Do not store above 30°C. Protect from light
Route of administration	Oral

Therapeutic indications	Indicated for the treatment of Type 2 Diabetes Mellitus (T2DM) as a monotherapy, adjunct to diet and exercise

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: Tenglyn 20mg

Composition: Teneligliptin hemipenta hydrobromide hydrate equivalent to Teneligliptin 20 mg

Pack size:3x 10 tablets

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

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

Manufacturer address: physical address of release site

Unique identifier: Not applicable

Special warnings/precautions or instructions for use: Read the package insert before use

The details of the primary pack include:

Brand name and strength: Tenglyn 20mg

Manufacturing details: batch number, manufacturing date and expiry date

Name of manufacturer: Cadila Healthcare 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 API was submitted in form of DMF.

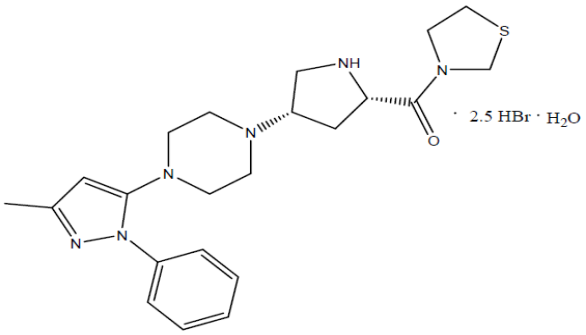
General Information

Teneligliptin hemipenta hydrobromide hydrate API is non-compendia.

Molecular formula: $C_{22}H_{34.5}N_6Br_{2.5}O_2S$

Chemical name:
3-{(2S,4S)-4-[4-(3-methyl-1-phenyl-1H-pyrazol-5-yl)piperazine-1-yl]pyrrolidine-2-ylcarbonyl} thiazolidine hemipentahydrobromide hydrate

Structure:



General properties

The active substance is an off-white to light brown powder and is freely soluble in water, 0.1N HCl, acetate buffer-pH 4.5, phosphate buffer -pH 6.8 and dimethyl sulfoxide, soluble in methanol, sparingly soluble in ethanol, practically insoluble in toluene. It shows polymorphism, the manufacturer consistently produces the same polymorphic form.

Manufacture

Teneligliptin hemipenta hydrobromide hydrate API manufacturer is Cadila Healthcare Limited, 5/1-B, G.I.D.C Industrial Estate, Ankleshwar, Gujarat, India – 393 002. The manufacturing complies with GMP requirements as evidenced by the GMP certificate issued by the Food and Drugs Control Administration of Gujarat State India. Teneligliptin hemipenta hydrobromide hydrate 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, solubility, identification, HBr content, polymorphism, water content, residue on ignition, heavy metals, related substances, assay,

residual solvents, 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 Teneligliptin hemipenta hydrobromide hydrate API is 24 months when packed in High molecular high density polythene transparent bag with storage condition 'Do not store above 30°C. Protect from light and moisture'.

Quality of the Finished Pharmaceutical Product

Formulation

Tenglyn 20mg is a light pink colored, round shaped, biconvex, film coated tablets, plain on both sides

Tenglyn 20mg contains the Teneligliptin hemipenta hydrobromide hydrate and other ingredients listed here after: mannitol, corn starch, hydroxy propyl cellulose (low substitute), hydroxypropyl cellulose, isopropyl alcohol, colloidal silicon dioxide, magnesium stearate, HPMC 2910/hypromellose, polyethylene glycol, castor oil, titanium dioxide, red iron oxide, and 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 manufacturer is Cadila Healthcare Limited located at PLOT NO.203-213, Kundaim Industrial Astate, Kundaim Village, Ponda, GOA 403115, India. The compliance of the site to TMDA GMP standards was confirmed through site inspection on 09 December, 2019.

Specifications

The FPP is non-compendia. 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 of API and colour agents, Average weight, Water content, Uniformity of Dosage units, Dissolution, Related substances, Assay, Microbial enumeration tests, and Test for specified Microorganisms. Compliance to the standard was established using batch analysis data and stability data.

Stability and container closure system

Stability studies were conducted on a 3 (three) batches of the finished product stored at 30 ± 2°C & RH: 75 ± 5% RH for 24 months and 40± 2°C & RH: 75% ± 5% RH for 6 months. Based on the stability data presented, the approved shelf-life is 24 months when stored in PVC/Aluminium blisters with storage condition 'Do not store above 30°C. Protect from light'.

Safety and efficacy information

Safety and efficacy of Tenglyn 20mg was established through a bioequivalence trial.

BE trial report number BA1686798-01 was submitted.

Study title	Single dose oral bioequivalence study of Teneligliptin Tablets 20 mg and 'TENELIA®' (Teneligliptin) Tablets 20 mg in healthy adult human subjects under fasting conditions	
Study design	An open label, randomized, two-period, two-treatment, two-sequence, crossover, balanced, single dose oral bioequivalence study	
Study site	Cliantha Research Limited Opposite Pushparaj Towers Nr. Judges Bungalows Bodakdev, Ahmedabad-380 054 Gujarat, India	
Study dates	28 Apr 2017 to 01 Jun 2017	
Primary objective	To compare and evaluate the oral bioavailability of Teneligliptin Tablets 20 mg with that of 'TENELIA®' (Teneligliptin) Tablets 20 mg in healthy, adult, human subjects under fasting conditions	
Secondary objective	To monitor the safety of the subjects	
Number of participants	Planned: 24 subjects + 2 standby Enrolled: 24 subjects + 2 standby Dosed: 24 subjects Withdrawn – 04 subjects (2 were replaced by standby subjects) Completed: 22 subjects, Bio-sample analyzed: 22 subjects Pharmacokinetic and statistical data analyzed: 22 subjects	
Monitored parameters	Tmax, Cmax, AUC0→t, AUC0→∞, AUC% Extrapolation Kel and T1/2	
Investigational medicinal products	Test Product	Reference product
	Strength: 20 mg Batch number: GE60357 Expiry date: 12/2016	Strength: 20 mg Batch number: 184X Expiry date: 09/2018
Analytical method	LC-MS/MS method was used for the determination of plasma concentration of analyte	
Statistical method	PROC MIXED SAS® statistical software (Version 9.4; SAS Institute Inc, USA).	

Efficacy results are summarized as follows:

Table of Geometric means, Results from ANOVA, Degrees of Freedom (DF) and derived CV (intra-individual):

Parameter	**Test**	**Reference**	**Ratio of Geometric Means**	**90 % Confidence interval**	**DF**	**CV (%)**

AUC0-t (ng.hr/mL)	1762.444	1760.089	100.13%	97.13%;103.23%	20	5.837
AUC0-inf (ng.hr/mL)	1852.969	1844.150	100.48%	97.33%;103.73%	20	6.107
Cmax (ng/mL)	162.309	162.456	99.91%	94.32%;105.83%	20	11.056

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, Teneligliptin Tablets 20 mg of Cadila Healthcare Limited, India is equivalent and interchangeable with TENELIA®' (Teneligliptin) Tablets 20 mg of Mitsubishi Tanabe Pharma Corporation & Daiichi Sankyo, Japan 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. Tenglyn 20mg 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;