THE UNITED REPUBLIC OF TANZANIA

MINISTRY OF HEALTH

TANZANIA MEDICINES AND MEDICAL DEVICES AUTHORITY

PUBLIC ASSESSMENT REPORT FOR LINAREN 5 (LINAGLIPTIN 5MG) TABLETS

Version number 1.0
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1. Introduction

Linaren 5 tablets is a triangular shaped light pink colored film coated tablet having a bisect line on one side containing the 5 mg linagliptin per each tablet. Linagliptin is a selective, orally administered, xanthine-based DPP-4 inhibitor. GLP-1 lowers blood glucose levels by augmenting the glucose-stimulated insulin release. Moreover, GLP-1 inhibits glucagon secretion, slows gastric emptying, and induces satiety. The plasma half-life of GLP-1 is limited to a few minutes because of rapid proteolytic degradation by the enzyme DPP-4. Inhibition of DPP-4 prolongs the half-life of active GLP-1 and thereby increases plasma insulin levels and lowers plasma glucose levels. Since GLP-1 activity ceases when the glucose concentration falls below 55 mg/dL, prolongation of the half-life of GLP-1 by DPP-4 inhibitors bears little risk of hypoglycaemia. Linagliptin is a selective, competitive, reversible inhibitor of human DPP-4 with a 50% Inhibitor Concentration (IC50) of 1 nM. The therapeutic dose of linagliptin will be 5 mg. Linagliptin is predominantly excreted unchanged via the faeces. Renal excretion is a minor pathway of elimination of linagliptin at therapeutic doses. Thus, linagliptin is especially suited for the treatment of patients with renal impairment without the need for dose adjustment. Linaren 5 tablets is approved in Tanzania for use in all ages.

Product details

Registration number	TAN 23 HM 0278
Brand name	Linaren 5
Generic name, strength, and form	Each film coated tablet contains Linagliptin 5 mg
ATC classification	Al0BH05 (dipeptidyl peptidase 4 (DPP-4) inhibitors)
Distribution category	POM
Country of origin	Bangladesh
Associated product	N/A
Marketing Authorization Holder	Neomedic Limited. Neomedic Limited Unit 2, 1A leavesden Road, Watford, WD24 5FR. United Kingdom
Local Technical Representative	Salama Pharmaceuticals Ltd. P. O. Box - 65235, Dar es Salaam, Tanzania.

1.1 Assessment procedure

The application for registration of Linaren 5 was submitted on 13/11/2020. The product underwent full assessment. Assessment was completed in 4 (four) rounds of evaluation and the product was registered on 01/06/2023.

1.2 Information for users

Visual description of the finished product	Triangular shaped light pink colored film coated tablet having a bisect line on one side

Primary packing material	Alu/Alu strips
Secondary packing materials	Carton
Shelf-life and storage condition	36 months, Do not store above 30°C.
Route of administration	Oral
Therapeutic indications	Linagliptin is indicated in the treatment of type-2 diabetes mellitus to improve glycaemic control in adults: As monotherapy: ● in patients inadequately controlled by diet and exercise alone and for whom Metformin is inappropriate due to intolerance, or contraindicated due to renal impairment. As combination therapy: ● in combination with Metformin when diet and exercise plus Metformin alone do not provide adequate glycaemic control. ● in combination with a Sulphonylurea and Metformin when diet and exercise plus dual therapy with these medicinal products do not provide adequate glycaemic control. ● in combination with Insulin with or without Metformin, when this regimen alone, with diet and exercise, does not provide adequate glycaemic control.

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.

Container labels
The product label information is presented in <English/Swahili>. Details in the secondary pack label include:
Brand name:
Composition: <generic name & strength, list of excipients (if applicable)>
Pack size: <primary & secondary pack>
Manufacturing details: <batch number, manufacturing date, expiry date>
Storage conditions: <state the condition as it appears on the label>
Manufacturer address: <physical address of release site>
Unique identifier: <state the unique identification used>
Special warnings/precautions or instructions for use: <include warnings or IFU if applicable>

The details of the primary pack include:

Brand name and strength:
Manufacturing details: <batch number, manufacturing date, expiry date>
Name of manufacturer: <name only>

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/currently not available>.

3. Scientific discussion

Quality of Active Pharmaceutical Ingredient

General Information

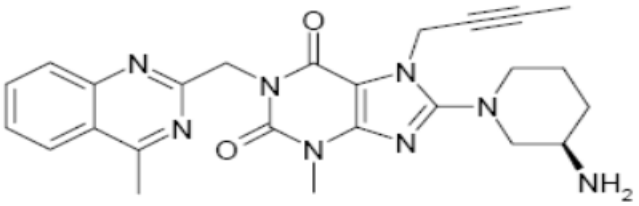
Linagliptin API is non-compendia.

Molecular formula: $C_{25}H_{28}N_8O_2$

Chemical name:

8-[(3R)-3-aminopiperidin-1-yl]-7-(but-2-yn-1-yl)-3-methyl-1-[(4-methylquinazolin-2-yl) methyl]-3,7-dihydro-1H-purine-2,6-dione.

Structure:



General properties

Linagliptin is a is a white to yellowish crystalline solid substance. It is slightly hygroscopic, but water uptake does not change the crystal modification. It is very soluble in aqueous media (> 1 mg/ml) over the entirecphysiological pH range. It is soluble in methanol, sparingly soluble in ethanol and very slightly soluble in isopropanol and acetone.

The active substance simultaneously exists in two polymorphic forms, which are enantiotropically related and which reversibly convert into each other approximately at room temperature. The two polymorphic forms do not differ with regard to biopharmaceutical properties.

Manufacture

Linagliptin API manufacturer is Lee Pharm a Limited, Sy No. IO/G-1, Gadda Potharam (Vi llage), J iru1aram (Manda!), Medak (District) Telangana, 502319, India.The manufacturing complies with GMP requirements as evidenced by the GMP certificate issued by the Drugs Control Administration, Government of Telangana. Linagliptin 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 (IR and HPLC), Loss on drying, Sulphated ash, heavy metals, related substance, Assay, Melting range, Enantiomer content, and Residual solvents. Compliance to these specifications were established via batch analysis data and stability studies.

Stability and container closure system

The re-test period of Linagliptin API is 60 months when packed in triple laminated clear low-density polyethylene bag with storage condition 'Do not store above 30^{o}C'.

Quality of the Finished Pharmaceutical Product

Formulation

Linaren 5 is a triangular shaped light pink colored film coated tablet having a bisect line on one side.

Linaren 5 contains the Linagliptin other ingredients listed here after: Maize Starch, Mannitol, Copovidone K 28, Pregelatinised Starch, Iron Oxide Red, Magnesium Stearate, Opadry II 85G58977 White, 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 manufacturers are Incepta Pharmaceuticals Ltd., Dewan Idris Road, Bara Rangamatia, Zirabo, Ashulia, Savar, Dhaka, Bangladesh. The compliance of the sites to TMDA GMP standards was confirmed through site inspection on DD/MM/YYYY.

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 (HPLC and UV), Disintegration, Dissolution, Average weight, Assay (HPLC), related substance (HPLC), Uniformity of dosage units by content uniformity, 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 3(three) 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 strips with storage condition 'Do not store above 30°C'.

Safety and efficacy information

Safety and efficacy of Linaren 5 was established through bioequivalence trial.

BE trial report number LIN/GL/12 was submitted.
In case of BE:

Study title	A Randomized, Open Label, Balanced, Two-Treatment, Two-Period, Two-Sequence, Single Dose, Crossover, Bioequivalence Study of linatab tablet (Linagliptin tablets 5 mg) of Incepta Pharmaceuticals Ltd. Compared with tradjenta (Linagliptin tablets 5 mg) of Boehringer Ingelheim Pharmaceuticals, INC.in Normal, Healthy Adult, Human Subjects Under Fasting Condition
Study design	An open-label, balanced, randomized, two-treatment, single-period, crossover, single oral dose, bioequivalence study under fasting condition
Study site	<u>Clinical study site:</u> RAPTIM RESEARCH LIMITED A-242, T.T.C. Industrial Area, Mahape M.I.D.C., Navi Mumbai-400 701, India. <u>Bioanalytical study site:</u> RAPTIM RESEARCH LIMITED A-242, T.T.C. Industrial Area, Mahape M.I.D.C., Navi Mumbai-400 701, India.

<table>
<tr><td>Study dates</td><td colspan="2"><table>
<tr><th>Activities</th><th>Dates</th></tr>
<tr><td>Period I (dosing)</td><td>05/02/2019</td></tr>
<tr><td>Period II (dosing)</td><td>26/02/2019</td></tr>
<tr><td>Analysis (start date)</td><td>15/03/2019</td></tr>
<tr><td>Analysis (completion date)</td><td>28/03/2019</td></tr>
</table></td></tr>
<tr><td>Primary objective</td><td colspan="2">To assess whether the test product was bioequivalent to reference product based on the evaluation of Cmax and AUC for Linagliptin</td></tr>
<tr><td>Secondary objective</td><td colspan="2">Descriptive statistics for pharmacokinetic (PK) parameter - Tmax.
Assessment of safety and tolerability profile of test and reference products</td></tr>
<tr><td>Number of participants</td><td colspan="2">Planned-22 subjects
Enrolled-22 subjects
Dosed-22 subjects
Withdrawn - 00 subject
Bio-sample analyzed -22 subjects
Pharmacokinetic and statistical data analyzed – 22 subjects</td></tr>
<tr><td>Monitored parameters</td><td colspan="2">Tmax, Cmax, AUC0→t, AUC0→∞, AUC% Extrapolation Kel and T1/2</td></tr>
<tr><td rowspan="2">Investigational medicinal products</td><td>Test Product</td><td>Reference product</td></tr>
<tr><td>Strength: 5mg
Batch number: 19006
Expiry date: 07/2020</td><td>Strength: 5mg
Batch number: ZR7042
Expiry date: 01/2010</td></tr>
<tr><td>Analytical method</td><td colspan="2">High Pressure Liquid chromatography – MS/MS – detector (LC-MS/MS) method was used for the determination of plasma concentrations of analyte</td></tr>
<tr><td>Statistical method</td><td colspan="2">SAS® 9.2 (SAS Institute Inc., USA) procedure</td></tr>
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Efficacy results are summarized as follows:

LINAGLIPTIN						
Pharmacokinetics Parameters	**Geometric Mean**		**Ratio(T/R) %**	**Intra Subject C.V(%)**	**Power(%)**	**90 % Confidence Interval(%)**
	Test(T)	**Reference(R)**				
C_{max} (pg/ml)	2712.44	2544.2	105.33	16.33	100.00	97.0-118.22
Auc_{0-t} (pgxhr/ml)	19543.44	19201.52	101.78	20.75	100.00	90.64-105.1
Auc_{0-inf} (pgxhr/ml)	21422.08	20721.5	103.38	22.94	100.00	96.43-105.2

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, Linaren 5

Tablets is equivalent and interchangeable with Tradjenta (Linagliptin tablets 5 mg) of Boehringer Ingelheim Pharmaceuticals, 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. Linaren 5 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 labels;

Primary pack label;

Secondary pack label;