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MINISTRYOFHEALTH

TANZANIAMEDICINES ANDMEDICALDEVICESAUTHORITY

PUBLIC ASSESSMENT REPORT FOR CARVILIN - 12.5 (CARVEDILOL USP 12.5 MG) TABLETS

Version number 01
3rd January, 2023

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1. Introduction

Carvilin-12.5is a generic medicine of coreg® 25 mg (carvedilol tablets 25 mg) of glaxosmithkline, USA. Carvilin-12.5 is an antihypetensive medicine belonging to C07AG02 Cardiovascular System - Beta blocking agents' group. Carvilin-12.5 is a vasodilatory non-selective beta-blocker, which reduces the peripheral vascular resistance by selective alpha 1- receptor blockade and suppresses the renin-angiotensin system through non-selective beta-blockade. Carvilin-12.5is approved in Tanzania for use in adults and elderly.

1.1 Product details

Registration number	TAN 21 HM 0283
Brand name	Carvilin-12.5
Generic name, strength and form	Carvedilol 12.5 mg film coated tablets
ATC classification	C07AG02 Cardiovascular System - Beta blocking agents
Distribution category	POM
Country of origin	India
Associated product	
Marketing Authorization Holder	Lincoln Pharmaceuticals Limited, TrimuL Estate, Khantraj, TALUKA: Kalol, District: Gandhinagar, Gujarat, **INDIA.** Email: info@lincolnpharma.com
Local Technical Representative	Heko Pharmacy Ltd P. O. BOX 2657, Plot No.32/57, Sikukuu/Tandamti Street, Kariakoo, **DAR ES SALAAM.** Email: hekopharmacy@cats-net.com

1.2 Assessment procedure

The application for registration of Carvilin-12.5 was submitted on <DDMMYYYY>. The product underwent full assessment. Assessment was completed in <number> rounds of evaluation. Carvilin-12.5 was registered on 20th August, 2021

1.3 Information for users

Visual description of the finished product	Orange coloured, round shaped, biconvex, film coated tablet, breakline on one side and plain on other side
Primary packing material	Alu-PVC Blister
Secondary packing materials	Carton box
Shelf-life and storage condition	36 months Store below 30ºC. Protect from light
Route of administration	Oral
Therapeutic indications	Carvedilol is indicated for treatment of mild-to-severe chronic heart failure of ischemic or cardiomyopathic origin, usually in addition to diuretics, ACE inhibitors and digitalis. Carvedilol is also indicated in left ventricular dysfunction following myocardial infarction and for the management of essential hypertension as alone or in combination with other antihypertensive agents, especially thiazide-type diuretics

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: Carvilin-12.5

Composition: Carvedilol 12.5 mg, Lactose Monohydrate, Microcrystalline Cellulose, Colloidal Anhydrous Silica, Crospovidone, Magnesium Stearate, Colour Sunset Yellow Orange SC-SP-2029, Isopropyl Alcohol, Dichloromethane.

Pack size: 2 x 14 tablets
Manufacturing details: <batch number, manufacturing date, expiry date>
Storage conditions: Store below 30OC. Protect from light
Manufacturer address: Lincoln Pharmaceuticals Limited, Trimul Estate, Khatraj, Taluka: Kalol, District: Gandhinagar, Gujarat, India
Unique identifier: NA
Special warnings/precautions or instructions for use: <include warnings or IFU if applicable>

The details of the primary pack include:
Brand name and strength: Carvilin-12.5
Manufacturing details: <batch number, manufacturing date, expiry date>
Name of manufacturer: Lincoln Pharmaceuticals 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

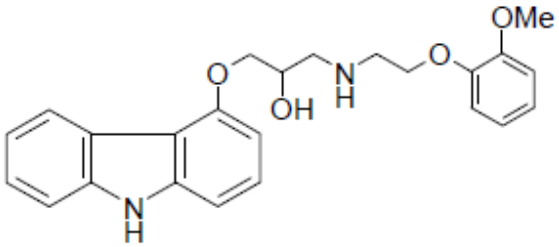
3. Scientific discussion

Quality of Active Pharmaceutical Ingredient(s)

Information on quality of the API was submitted in form of Full details

General properties
Carvedilol API is compendia in USP.
Molecular formula: C24H26N2O4
Chemical name: (2RS)-1-(9H-Carbazol-4-yloxy)-3-[[2-(2-methoxyphenoxy) ethyl] amino]propan-2-ol

Structure:



White or almost white crystalline powder that is practically insoluble in water and dilute acids, slightly soluble in alcohol. Carvedilol is classified as BCS class 2 molecule which is low soluble API according to BCS. Carvedilol is known to exhibit polymorphism. Form II is consistently produced by CTX Lifesciences Pvt., Limited.

Manufacture

The API manufacturing site, CTX Life sciences Pvt. Ltd., Block No. 251-252, Sachin-Magdalla Road, GIDC, Sachin, Surat – 394 230, Gujarat, India was noted to comply with WHO GMP requirements as evidenced by the GMP certificate issued by Food and Drugs Control Administration, Gujarat State. Carvedilol 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 US, in-house standards and ICHQ3A. The parameters monitored during quality control are: Description, solubility, identification, (by IR and HPLC), loss on drying, heavy metals, residue on ignition, related substances9HPLC), residual solvents (GC), Benzene content (GC), assay (HPLC). Compliance to these specifications were established via batch analysis data and stability studies.

Stability and container closure system

The re-test period of Carvedilol API is 72 months when packed in low-density polyethylene (LDPE) bag which is closed with a twist tie. This bag is inserted in a second LDPE bag, which is also closed with a twist tie with a plastic fastener and stored at 25°C ± 2°C & 60 % ± 5% RH.

Quality of the Finished Pharmaceutical Product

Formulation

Carvilin-12.5 is an orange coloured, round shaped, biconvex, film coated tablet, breakline on one side and plain on other side. Carvilin-12.5 contains <API> and other

ingredients listed here after Lactose Monohydrate, Microcrystalline Cellulose, Colloidal Anhydrous Silica, Crospovidone, Magnesium Stearate, Colour Sunset Yellow Orange SC-SP-2029, Isopropyl Alcohol, Dichloromethane The quantities of all ingredients are confirmed to be in line with the recommendations of Handbook of Pharmaceutical Excipients, Edition 8^{th} in terms of function and quantities. Ingredient, Lactose Monohydrate is of safety concern therefore appropriate warnings were included in the product label.

Manufacture

The finished product was manufactured at Lincoln Pharmaceuticals Limited, Trimul Estate, Khatraj, Tal. Kalol, Dist. Gandhinagar, Gujarat, India. The compliance of the site to TMDA GMP standards was confirmed through site inspection on 25 - 26 February, 2015.

Specifications

The FPP is USP The manufacturer controls the quality of the finished product as per USP, in-house and ICHQ3B requirements. The parameters monitored during quality control are: Description, Identification, Average Weight, Uniformity of dosage units (By content uniformity), Diameter, Thickness, Disintegration test, Dissolution (By UV), related substances, Assay (By HPLC) 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 three batches of the finished product stored at 30° ± 2°C & 75 % ± 5% RH for 36 months and 40° ± 2°C & 75% ± 5% RH for 6 months. Based on the stability data presented, the approved shelf-life is 36 months when stored in Alu-PVC Blister at 30^{O}C.

Safety and efficacy information

Safety and efficacy of Carvilin-12.5 was established through <bioequivalence trial. BE trial report number **CAR_211_16** was submitted.

In case of BE:

Study title	A randomized, two-way crossover, open label, balanced, twotreatment, two-period, two-sequence, single dose, oral bioequivalence study for carvedilol tablets USP 25 mg of lincoln pharmaceuticals ltd., India with coreg® 25 mg (carvedilol tablets 25 mg) of glaxosmithkline, USA in 24 healthy, adult, male, human subjects under fasting conditions.

<table>
<tr><td>Study design</td><td>randomized, open label, balanced, two-treatment, two-period, two-sequence, single dose, two-way crossover, oral bioequivalence study under fasting conditions with at least 07 days washout period between each drug administration. Subjects were confined in the facility from at least 11 hours before drug administration to 24 hours after drug administration in each period if the subjects do not suffer from any adverse event</td></tr>
<tr><td>Study site</td><td>Om Sai Clinical Research Pvt. Ltd.
C.S.T. No. 379/1-6, Karnal Chowki, Peth Bhag, Sangli – 416416, Maharashtra,
India.</td></tr>
<tr><td>Study dates</td><td><table><tr><th>Activities</th><th>Dates</th></tr><tr><td>Period I (dosing)</td><td>18/04/2016 to 20/04/2016</td></tr><tr><td>Period II (dosing)</td><td>25/04/2016 to 27/04/2016</td></tr><tr><td>Analysis (start date)</td><td>28/04/2016</td></tr><tr><td>Analysis (completion date)</td><td>09/05/2016</td></tr></table></td></tr>
<tr><td>Primary objective</td><td>The objective of the study was to compare the bioavailability of the Carvilin-12.5 manufactured by Lincoln Pharmaceuticals Limited (test drug) with the reference formulations coreg® 25 mg (carvedilol tablets 25 mg) of glaxosmithkline, USA</td></tr>
<tr><td>Secondary objective</td><td>To monitor the safety of the subjects</td></tr>
<tr><td>Number of participants</td><td>24</td></tr>
<tr><td>Monitored parameters</td><td>AUC, Cmax, Tmax, T1/2, Kel</td></tr>
<tr><td rowspan="2">Investigational medicinal products</td><td>Test Product</td><td>Reference product</td></tr>
<tr><td>Strength: 25 mg
Batch number:TI5006
Expiry date:11/2018</td><td>Strength: 25 mg
Batch number: RJ0516
Expiry date:03/2018</td></tr>
<tr><td>Analytical method</td><td>LC/MS/MS</td></tr>
<tr><td>Statistical method</td><td>SAS® Software (Version 9.2).</td></tr>
</table>

Efficacy results are summarized as follows:

Parameter	Test	Reference	% Ratio of geometric means	90 % Confidence interval	DF	CV (%)

AUC0-t (units)	50352.70	48888.98	102.99	95.59 – 110.97	22	16.28
AUC0-inf (units)	51494.79	49987.38	103.02	95.79 – 110.78	22	16.04
Cmax (units)	6022.812	5843.551	103.07	93.88 – 113.15	22	25.41

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, Carvilin-12.5 is equivalent and interchangeable with Coreg® 25 mg (carvedilol tablets 25 mg) of glaxosmithkline, USA under acceptable in vivo experimental conditions.

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. Carvilin-12.5is 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

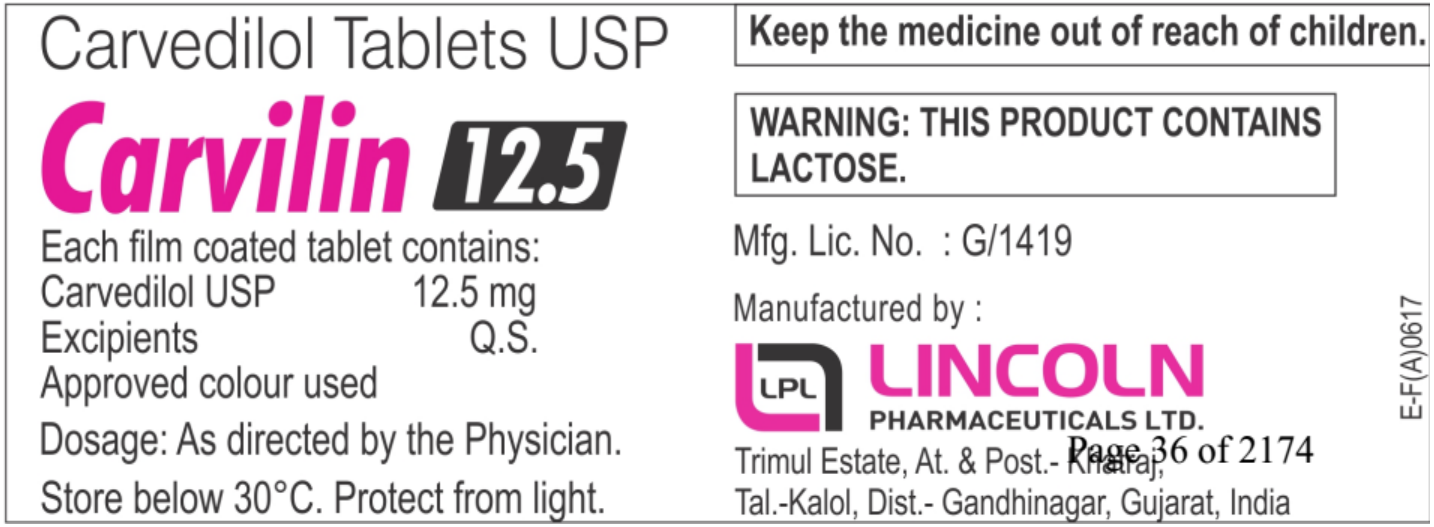
Re-registration applications

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




2 x 14 Tablets
Carvedilol Tablets USP
Carvilin 12.5
LINCOLN
PHARMACEUTICALS LTD.
Carvilin 12.5
E-C0617
Carvilin 12.5
Carvilin 12.5
Each film coated tablet contains:
Carvedilol USP 12.5 mg
Excipients Q.S.
Approved colour used
Dosage : As directed by the Physician.
Store below 30°C. Protect from light.
Keep the medicine out of reach of children.
WARNING: THIS PRODUCT CONTAINS LACTOSE.
POM
8 906063 984849
Manufactured by :
LINCOLN
PHARMACEUTICALS LTD.
Tarnul Estate, At. & Post.- Khatraj,
Tal.-Kalol, Dist.- Gandhinagar, Gujarat, India
E-mail : info@lincolnpharma.com
Website : www.lincolnpharma.com
Mfg. Lic. No. : G/1419
Reg. No. :
Batch No. :
Mfg. Date :
Exp. Date :
Do not Varnish Here