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MINISTRYOFHEALTH

TANZANIAMEDICINES ANDMEDICALDEVICESAUTHORITY

PUBLIC ASSESSMENT REPORT FOR ENDULIN CART ™ (INSULIN GLARGINE 100 IU/ML) SOLUTION FOR INJECTION

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1. Introduction

Endulin Cart is a generic medicine. Endulin Cart is an antidiabetic medicine belonging to A10AE04; Drugs used in diabetes, insulins and analogues for injection, long-acting. Endulin Cart exerts is activity by regulation of glucose metabolism. In addition insulin has several anabolic and anti-catabolic actions on a variety of different tissues. Within muscle tissue this includes increasing glycogen, fatty acid, glycerol and protein synthesis and amino acid uptake, while decreasing glycogenolysis, gluconeogenesis, ketogenesis, lipolysis, protein catabolism and amino acid output. The typical activity profile (glucose utilisation curve) following subcutaneous injection is illustrated below by the heavy line. Variations that a patient may experience in timing and/or intensity of insulin activity are illustrated by the shaded area. Individual variability will depend on factors such as size of dose, site of injection temperature and physical activity of the patient. Endulin Cart is approved in Tanzania for use in adults and elderly.

1.1.Product details

Registration number	TAN 21 HM 0261
Brand name	Endulin Cart
Generic name, strength and form	insulin glargine 100 IU/ml Solution for injection
ATC classification	Drugs used in diabetes, insulins and analogues for injection, long-acting. ATC Code: A10AE04
Distribution category	POM
Country of origin	India
Associated product	State any other product of formulation, strength or site that is linked or associated with the product if applicable
Marketing Authorization Holder	Mylan Pharmaceuticals Private Limited, Plot no.: 1-A/2, MIDC Industrial Estate, Taloja, Panvel (Raigad), PIN – 410208, Maharashtra **INDIA**
Local Technical Representative	Pyramid Pharma Limited, Mikocheni Street, Plot 1176, P.O. Box 16215, **DAR ES SALAAM**

1.2. Assessment procedure

The application for registration of Endulin Cart was submitted on 17th August, 2015 .The product underwent full assessment. Assessment was completed in two rounds of evaluation. Endulin Cart was registered on 2nd August, 2019

1.3. Information for users

Visual description of the finished product	Clear colourless solution
Primary packing material	3 ml in Type I USP glass cartridge
Secondary packing materials	carton box
Shelf-life and storage condition	24 months 2ºC – 8ºC
Route of administration	Subcutaneous
Therapeutic indications	Treatment of diabetes mellitus in adults, adolescents and children aged 6 years and above

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: Endulin Cart

Composition: Insulin Glargine, m-Cresol, Glycerol, Zinc and Water for Injection
Pack size: 3 ml
Manufacturing details: <batch number, manufacturing date, expiry date>
Storage conditions: 2ºC – 8ºC
Manufacturer address: Biocon Limited, Plot no.: 2 – 4, Phase IV, Bommasandra – Jigan Link Road, Bommasandra Post, Bangalore – 560 099, 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: Endulin Cart, 100 IU/ml Solution for injection
Manufacturing details: <batch number, manufacturing date, expiry date>
Name of manufacturer: Biocon 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.
Describe any approved deviation to the requirements and the justification for the deviation.

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
Insulin Glargine API is compendia in USP/BP
Molecular formula: $C_{267}H_{404}N_{72}O_{78}S_6$
Chemical name: 21^{A}-Glycine-31^{B}-L-arginine-32^{B}-L-arginine-insulin (human)

Structure:



Insulin Glargine drug substance is a white or almost white powder. Solubility: Should be soluble in 0.1 M Hydrochloric acid. Iso-electric point: Isoelectric point of Insulin Glargine is close to 7.0.

Mylan's Insulin Glargine was compared with reference medicinal product for in vitro metabolic and mitogenic potency, for in vitro insulin and insulin growth factor-1 (IGF-1) receptor binding. Insulin Glargine and reference product were equipotent in in vitro metabolic and mitogenic assays; had the same in vitro binding characteristics and affinity for insulin receptor and IGF-1 receptors. Therefore, Insulin Glargine was found to be pharmacodynamically equivalent to reference product.

Manufacture

The API manufacturing site, M/s Biocon Limited, 20th KM. Hosur Road, Electronics City, Bangalore - 560 100, India was noted to comply with WHO GMP requirements as evidenced by the GMP certificate issued by <state the issuing authority>.

Insulin Glargine API is manufactured by fermentation 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 BP, In-house standards and ICHQ3A. The parameters monitored during quality control are: Appearance , Solubility, Identification by RT comparison (by HPLC), Identification by peptide mapping, High molecular weight, impurities (by size exclusion chromatography), Single chain precursor (by HPLC), Zinc content (by atomic absorption spectrometry), Loss on drying, Sulphated ash, Related compounds (by HPLC), Glycosylated impurity, Assay (by HPLC), Host cell derived proteins, Host cell derived DNA, Residual solvents (by GC) Bacterial endotoxins and microbial limit test. Compliance to these specifications were established via batch analysis data and stability studies.

Stability and container closure system

The re-test period of Insulin Glargine API is 12 months when packed in Air tight dry depyrogenated amber colored glass bottles of USP Type-III and stored at -18°C or below in a freezer

Quality of the Finished Pharmaceutical Product

Formulation

Endulin Cart is a Clear colourless solution packed in 3 ml in Type I USP glass cartridge. Endulin Cart contains Insulin Glargine and other ingredients listed here after m-Cresol, Glycerol, Zinc and Water for Injection. 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.

Manufacture

The finished product was manufactured at Biocon Limited, Plot no.: 2 – 4, Phase IV, Bommasandra – Jigan Link Road, Bommasandra Post, Bangalore – 560 099, India. The compliance of the site to TMDA GMP standards was confirmed through site inspection on 2019.

Specifications

The FPP is compendia in BP/USP. The manufacturer controls the quality of the finished product as per BP, in-house and ICHQ3B requirements. The parameters monitored during quality control are: Description, Identification, pH of the solution, High molecular weight impurities (size exclusion chromatography), Zinc content (AAS), m-Cresol content, Particulate contamination (visible particulate), Extractable volume, Assay (HPLC), Related compounds, Bacterial endotoxins, Sterility, Particulate contamination, Seal integrity. 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 2°C - 8°C for 24 months and 25°C ± 2°C, 60 ± 5% RH for 6 months. Based on the stability data presented, the approved shelf-life is 24 months when stored in 3 mL colourless tubular glass (USP Type I) cartridges sealed using lined seals and plugged with plunger stoppers at temperature between 2ºC to 8ºC.

Safety and efficacy information

Safety and efficacy of Endulin Cart was established through clinical studies.The summary of all studies performed are listed in below tables.

Type of Study	Study Identifier	Objective(s) of the Study	Study Design and Type of Control	Test Product(s) Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
Phase I	GLARGCT100111	**Primary:** To compare the relative PK and PD properties of Mylan's Insulin Glargine, Lantus® (US-RLD) and , Lantus® sourced from the EU) **Secondary:** To evaluate single dose safety and local tolerability of the 3 products	Single-center, randomized, double-blind, single-dose, 3-way crossover euglycemic clamp; active control (Lantus®).	**Test product:** Mylan's Insulin Glargine **Reference Products:** , Lantus® US-RLD and , Lantus® sourced from the EU; Single dose of 0.4 IU/kg of each product at 3 separate visits. **Dose Regimen:** 3 single doses of 0.4 U/kg; each administration separated from the other by 5-28 days. **Route of Administration:** Subcutaneous.	114 randomized	Type 1 diabetes mellitus patients	13.5 weeks	Completed
Phase 3	CLG031/BIO012/ DM/GLA/2007	• To demonstrate non-inferiority with respect to decrease in HbA1C in patients with type 1 diabetes treated with recombinant Mylan's Insulin Glargine as compared to , Lantus® combined with pre-meal soluble insulin. • To demonstrate comparable equivalence of recombinant Mylan's Insulin Glargine to Lantus® with respect to safety.	Open- Label, Randomized, Multi-centric Safety/Efficacy Study; Active control	Mylan's Insulin Glargine or , Lantus®; OD for 12 weeks (after 4-week run-in on , Lantus®); SC	226 (entered run in); 215 (randomized)	Type 1 Diabetes Mellitus patients	12 weeks	Completed

Phase 1 study: GLARGCT100111

Study title	A single center, randomized, double-blind, single dose, 3-way crossover euglycemic clamp study in subjects with type 1 diabetes mellitus to compare the relative pharmacokinetic and pharmacodynamic properties of Basalog® 100 IU/mL with Lantus® 100 U/mL
Study design	This study was designed to meet the regulatory requirements for demonstrating PK and PD similarity between Insulin Glargine and Lantus® (sourced from US and EU). The study was conducted at Profil Institut für Stoffwechselforschung GmbH, Germany.

Study site	Profil Institut für Stoffwechselforschung GmbH, Hellersbergstr. 9; 41460 Neuss, Germany	
Study dates	08 Nov 2011 – 07 Mar 2012	
Primary objective	The primary objective was to compare the relative pharmacokinetic and pharmacodynamic properties of Basalog 100 IU/mL with LantusÒ 100 U/mL (EU RP and US RLD) in subjects with type 1 diabetes mellitus.	
Secondary objective	The secondary objective was to assess the single dose safety and local tolerability of Basalog 100 IU/mL relative to Lantus 100 U/mL (EU RP and US RLD)	
Number of participants	Enrolled: 114 Completed the study: 112 Statistical analysis: 110	
Monitored parameters	Primary endpoints: PK endpoints: AUCins.0-30h; Cins.max. PD endpoints: AUCGIR0-30h; GIRmax. Secondary endpoints: PK endpoints: AUCins.0-6h, AUCins.6-30h, AUCins.0-∞, tmax, t½ and terminal elimination rate constant (λz). PD endpoints: AUCGIR0-6h, AUCGIR6-30h and tGIRmax. Safety endpoints: AEs, hematology, biochemistry, urinalyses, physical examination, vital signs, ECGs, blood glucose and local tolerability on injection	
Investigational medicinal products	Test Product	Reference product
	Strength: Insulin glargine (Basalog®) 100 IU/mL in 10.0 mL Batch number: V11DEVB-0005 Expiry date: 01/2013	Strength: Insulin glargine (Lantus) 100 U/mL in 3.0 mL cartridges Batch number: 1F677A Expiry date: 02/2014
Analytical method		
Statistical method	SAS® System for Windows (Version 9.3)	

Efficacy results are summarized as follows

Pharmacokinetics

Parameter	Product(s)	N*	Geo Mean	Geo Mean ratio[1]	CI 90%	CI 95%
$AUC_{ins.0-30h}$ [pmol*h/L]	Lantus® (EU RP)	74	3635		3357; 3936	3305; 3998
	Lantus® (US RLD)	65	3609		3326; 3916	3273; 3979
	Basalog®	61	3696		3403; 4015	3348; 4080
	Lantus® (EU RP) vs. Lantus® (US RLD)	51		1.01	0.95; 1.07	0.94;1.08
	Basalog® vs. Lantus® (EU RP)	48		1.02	0.96; 1.08	0.94; 1.10
	Basalog® vs. Lantus® (US RLD)	44		1.02	0.96; 1.09	0.95; 1.11
$C_{ins.max}$ [pmol/L]	Lantus® (EU RP)	94	201		188; 216	185; 218
	Lantus® (US RLD)	87	199		185; 213	183; 216
	Basalog®	89	198		185; 212	182; 215
	Lantus® (EU RP) vs. Lantus® (US RLD)	83		1.01	0.95; 1.08	0.94; 1.09
	Basalog® vs. Lantus® (EU RP)	84		0.98	0.92; 1.05	0.91; 1.06
	Basalog® vs. Lantus® (US RLD)	78		1.00	0.93; 1.06	0.92; 1.08

The acceptance limits of 80 – 125% are met by the AUCins and Cins.max values. Furthermore, the safety profile of the test product is similar to that of reference product. Therefore, Endulin Cart is equivalent and interchangeable with Insulin glargine (Lantus) 100 U/mL in 3.0 mL cartridges under acceptable in vivo experimental conditions.

Pharmacodynamics

Parameter	Product(s)	N	Geo Mean	Geo Mean ratio[1]	CI 90%	CI 95%
$AUCGIR_{0-30h}$ [mg/kg]	Lantus® (EU RP)	107	988		860; 1135	837; 1166
	Lantus® (US RLD)	106	1022		889; 1174	866; 1206
	Basalog®	107	956		833; 1099	811; 1128
	Lantus® (EU RP) vs. Lantus® (US RLD)	104		0.97	0.85; 1.11	0.82; 1.14
	Basalog® vs. Lantus® (EU RP)	104		0.97	0.85; 1.11	0.82; 1.14
	Basalog® vs. Lantus® (US RLD)	103		0.94	0.82; 1.07	0.80; 1.10
GIR_{max} [mg/kg/min]	Lantus® (EU RP)	106	1.38		1.26; 1.51	1.23; 1.53
	Lantus® (US RLD)	105	1.40		1.28; 1.53	1.25; 1.56
	Basalog®	106	1.38		1.26; 1.52	1.24; 1.54
	Lantus® (EU RP) vs. Lantus® (US RLD)	102		0.98	0.90; 1.07	0.89; 1.09
	Basalog® vs. Lantus® (EU RP)	103		1.01	0.92; 1.10	0.91; 1.11
	Basalog® vs. Lantus® (US RLD)	102		0.99	0.91; 1.08	0.89; 1.10

The acceptance limits of 80 – 125% are met by the AUCGIR0-30h and GIRmax values. Furthermore, the safety profile of the test product is similar to that of reference product. Therefore, Endulin Cart is equivalent and interchangeable with Insulin glargine (Lantus) 100 U/mL in 3.0 mL cartridges 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. Endulin Cart 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	**Date**	**Description of update**	**Section(s) Modified**	**Approval date**

Annex I: Mock up label

