THE UNITED REPUBLIC OF TANZANIA

MINISTRY OF HEALTH

TANZANIA MEDICINES AND MEDICAL DEVICES AUTHORITY

PUBLIC ASSESSMENT REPORT FOR NIZACARD 1000 MG (RANOLAZINE 1000 MG) EXTENDED-RELEASE TABLETS

Version number 1.0
21 August 2023

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1. Introduction

NIZACARD 1000 is blue coloured, oblong shaped film coated tablets debossed with 'R19' on one side and 'H' on the other side contains Ranolazine equivalent to ranolazine 1000 mg per each tablet. Ranolazine is a novel small molecule of a new pharmacological class which is believed to have its anti-ischaemic and antianginal effects via inhibition of the late sodium current in cardiac cells with a resultant reduction of intracellular sodium and intracellular calcium overload. The clinical development programme for ranolazine commenced in 1985 with initial studies using intravenous (IV) and immediate release (IR) formulations. In order to maintain an effective plasma concentration, an extended release (ER) formulation was developed. There have been sponsorship and formulation changes subsequently. A prolonged release (PR) formulation has been proposed for registration. NIZACARD 1000 is approved in Tanzania for use only in adults.

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1.1 Product details

Registration number	TAN 23 H 0262
Brand name	NIZACARD 1000
Generic name, strength, and form	Each Extended-release tablet contains 1000mg of Ranolazine
ATC classification	Other cardiac preparations, ATC code: C01EB18
Distribution category	POM
Country of origin	India
Associated product	N/A
Marketing Authorization Holder	Hetero Labs Limited, Hetero Corporate, 7-2-A2, Industrial Estates, Sanath Nagar, Hyderbad-500 018, Telangana India
Local Technical Representative	Kas Medics Limited Umoja Complex, Plot No, 11, First Floor, Uf09 & Uf10, Vingunguti Industrial Area, along Nyerere Road Adjacent To 10 Wes Commercial Complex, Dar-Es-Salaam.

1.2 Assessment procedure

The application for registration of NIZACARD 1000 was submitted on DD/MM/YYYY. The product underwent full assessment. Assessment was completed in 3 (three) rounds of evaluation and the product was registered on 01 June 2023.

1.3 Information for users

Visual description of the finished product	Blue colored, oblong shaped film coated tablets debossed with ’R19’on one side and ‘H’on the other side
Primary packing material	Alu-PVC/PVdC Blister
Secondary packing materials	A printed carton box
Shelf-life and storage condition	24 months, store below 30°C
Route of administration	Oral

Therapeutic indications	Ranolazine Tablets is indicated for the treatment of chronic angina. Ranolazine Tablets may be used with beta-blockers, nitrates, calcium channel blockers, anti-platelet therapy, lipid-lowering therapy, ACE inhibitors, and angiotensin receptor blockers.

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: NIZACARD 1000

Composition: Each Extended-release tablet contains 1000mg of Ranolazine

Pack size: 3x10 tablets

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

Storage conditions: Store below 30°C

Manufacturer address: physical address of release site

Unique identifier: Not applicable

Special warnings/precautions or instructions for use: See enclosed leaflet

The details of the primary pack include:

Brand name and strength: NIZACARD 1000

Manufacturing details: batch number, manufacturing date and expiry date

Name of manufacturer: Hetero Labs 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

Information on the quality of the API was submitted in form of DMF.

Ranolazine

General Information

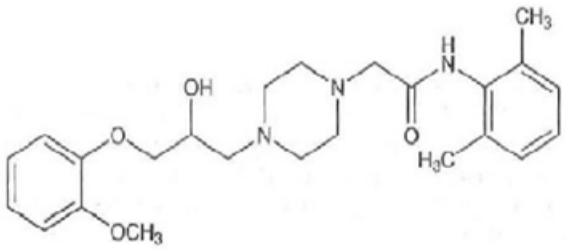
Ranolazine API is non-compendia.

Molecular formula: $C_{16}H_{19}N_3O_5S, 3H_2O$

Chemical name:

N-(2, 6-Dimethylphenyl)-2-[4-[2-hydroxy-3-(2-methoxyphenoxy) propyl] piperzin-1-yl] acetamide

Structure:



General properties

Ranolazineis a white or almost white granulated powder, which is soluble in water, very slightly soluble in alcohol, practically insoluble in fatty oils. It dissolves in dilute acids and dilute solutions of alkali hydroxides.

Ranolazine is a white to off-white solid, very slightly soluble in water. It is freely soluble in aqueous buffered solutions at pH levels below 4.4 and soluble in several organic solvents e.g., dichloromethane and methanol.

Ranolazine exhibits a chiral center and is obtained as a racemic mixture that consists of a 1:1 ratio of (R) and (S) enantiomers. This is confirmed by demonstrating that ranolazine does not exhibit any optical rotation of plane polarized light in polarimeter measurements. Both enantiomers exhibit pharmacological activity.

Regarding polymorphism, crystallisation studies were conducted using different solvents, crystallization conditions and vapor diffusion experiments. In these studies, three crystalline forms named as Form I, Form II, Form III and one amorphous form were identified. Form I is the only one that was thermodynamically stable, Form II and Form III are kinetically unstable. The synthetic process used for the synthesis of ranolazine has been shown to produce only Form I. Extreme conditions that are not relevant to the synthetic process are required to convert ranolazine to other solid-state forms (amorphous and two other crystalline forms, Form II and Form III).

Manufacture

Ranolazine API manufacturer is DASAMI LAB PRIVATE LIMITED, Survey No.405& 408, Veliminedu Village, Chityala Mandal, Nalgonda District, Telangana – 508114, India. The manufacturing complies with GMP requirements as evidenced by the GMP certificate issued by the Drugs Control Administration, Telangana. Ranolazine 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, residue on ignition, polymorphism, related substance (HPLC), assay, residual solvents, particle size, MPO content, and benzene content. Compliance to these specifications were established via batch analysis data and stability studies.

Stability and container closure system

The re-test period of Ranolazine API is 60 months when packed in transparent LDPE bag and place in black LDPE bag along with silica gel pack by hot sealed under nitrogen atmosphere. The primary packing material is placed in TLMB bag along with silica packed under nitrogen with storage condition ‘Preserve in tight, light-resistant containers. Store at 25°C, excursions permitted between 15°C and 30°C’.

Quality of the Finished Pharmaceutical Product

Formulation

NIZACARD 1000 is blue colored, oblong shaped film coated tablets debossed with ’R19’on one side and ‘H’ on the other side

NIZACARD 1000 contains the Ranolazine and other ingredients listed here after: methacrylic acid copolymer, microcrystalline cellulose, hypromellose, sodium hydrochloride, purified water, magnesium stearate, opadry II blue 85f505115 (polyvinyl alcohol-part. hydrolyzed,

macrogol/PEG, titanium dioxide, talc, FD&C blue #2/indigo carmine aluminum lake). 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 Hetero Labs Limited, Unit III, 22-110, IDA, Jeedimetla, Hyderabad, Telangana, India. 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 and ICH requirements. The parameters monitored during quality control are: Description, identification by HPLC and HPLC-PDA, average weight, water content, dissolution, uniformity of dosage units, related compounds, assay, and microbiological examination. Compliance to the standard was established using batch analysis data and stability data.

Stability and container closure system

Stability studies were conducted on three (3) batches of the finished product stored at 30±2℃ R.H. 75±5% for 24 months and 40±2℃R.H. 75±5% for 6 months. Based on the stability data presented, the approved shelf-life is 24 months when stored in Alu-PVC/PVdC Blister with storage condition 'Store below 30°C'.

Safety and efficacy information

Safety and efficacy of NIZACARD 1000 was established through a bioequivalence trial.

Study 1 (single dose, fasting, 1000 mg tablet)

BE trial report number 0798-17 was submitted.

Study title	An open label, balanced, randomized, two-treatment, two-period, two-sequence, crossover, single oral dose, bioequivalence study of Ranolazine extended-release tablets 1000 mg of Hetero Labs Limited comparing with RANEXA® (Ranolazine extended-release tablets) 1000 mg of Gilead Sciences, Inc., Foster City, CA 94404 in normal, healthy, adult, human subjects under fasting condition
Study design	An open label, balanced, randomized, two-sequence, two-treatment, two-period, crossover, single oral dose bioequivalence study in normal, healthy, adult, human subjects under fasting condition
Study site	Lambda Therapeutic Research Ltd., Lambda house, Plot No. 38, Survey no. 388, Near Silver Oak Club, S. G. Highway, Gota, Ahmedabad - 382481 Gujarat, India

Study dates	**Activities**	**Dates**
	Period I (dosing)	21st April 2018
	Period II (dosing)	25th April 2018
	Analysis (start date)	04th June 2018
	Analysis (completion date)	13th June 2018
Primary objective	To investigate the bioequivalence of test product relative to reference product after a single oral dose administration of Amoxicillin to healthy adults under fasting conditions	
Secondary objective	To monitor the safety and tolerability of a single dose of Ranolazine when administered in 24 healthy adult human subjects under fasting condition	
Number of participants	Planned-48 subjects Enrolled-48 subjects Dosed-48 subjects Withdrawn - 03 subjects Bio-sample analyzed -48 subjects Pharmacokinetic and statistical data analyzed – 45 subjects	
Monitored parameters	Tmax, Cmax, AUC0→t, AUC0→∞, AUC% Extrapolation Kel and T1/2	
Investigational medicinal products	Test Product	Reference product
	Strength: 1000 mg Batch number: E180360 Expiry date: 31/12/2019	Strength: 1000 mg Batch number: 3132234A Expiry date: 31/03/2020
Analytical method	High Pressure Liquid chromatography – MS/MS – detector (LC-MS/MS) method was used for the determination of plasma concentrations of analyte	
Statistical method	PROC MIXED of SAS® Version 9.3 (SAS Institute Inc., USA)	

Efficacy results are summarized as follows:

Parameters	Geometric Least Squares Means			90% Confidence Interval	Intra Subject CV (%)	Power (%)
	Test Product-T	Reference Product-R	Ratio (T/R) %			
lnC_{max}	1288.271	1182.195	109.0	97.83 - 121.39	31.1	96.0
$lnAUC_{0-t}$	13832.835	13595.805	101.7	90.47 - 114.42	34.0	93.1
$lnAUC_{0-\infty}$	14053.009	13689.339^	102.7	91.01 - 115.79	34.6	92.1

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, Ranolazine extended-release tablets 1000 mg of Hetero Labs Limited is equivalent and interchangeable with RANEXA® (Ranolazine extended-release tablets) 1000 mg of Gilead Sciences, Inc., Foster City, CA 94404 under acceptable in vivo experimental conditions.

Study 2 (single dose, fed, 1000 mg tablet)

<BE trial/comparative dissolution> report number <number> was submitted.
In case of BE:

Study title		
Study design		
Study site		
Study dates		
Primary objective		
Secondary objective		
Number of participants		
Monitored parameters		
Investigational medicinal products	Test Product	Reference product
	Strength: Batch number: Expiry date:	Strength: Batch number: Expiry date:
Analytical method		
Statistical method		

Efficacy results are summarized as follows:

Parameter	Test	Reference	% Ratio of geometric means	90 % Confidence interval	DF	CV (%)
AUC0-t (units)						
AUC0-inf (units)						
Cmax (units)						

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, <brand name> is equivalent and interchangeable with <comparator>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. NIZACARD tablets 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

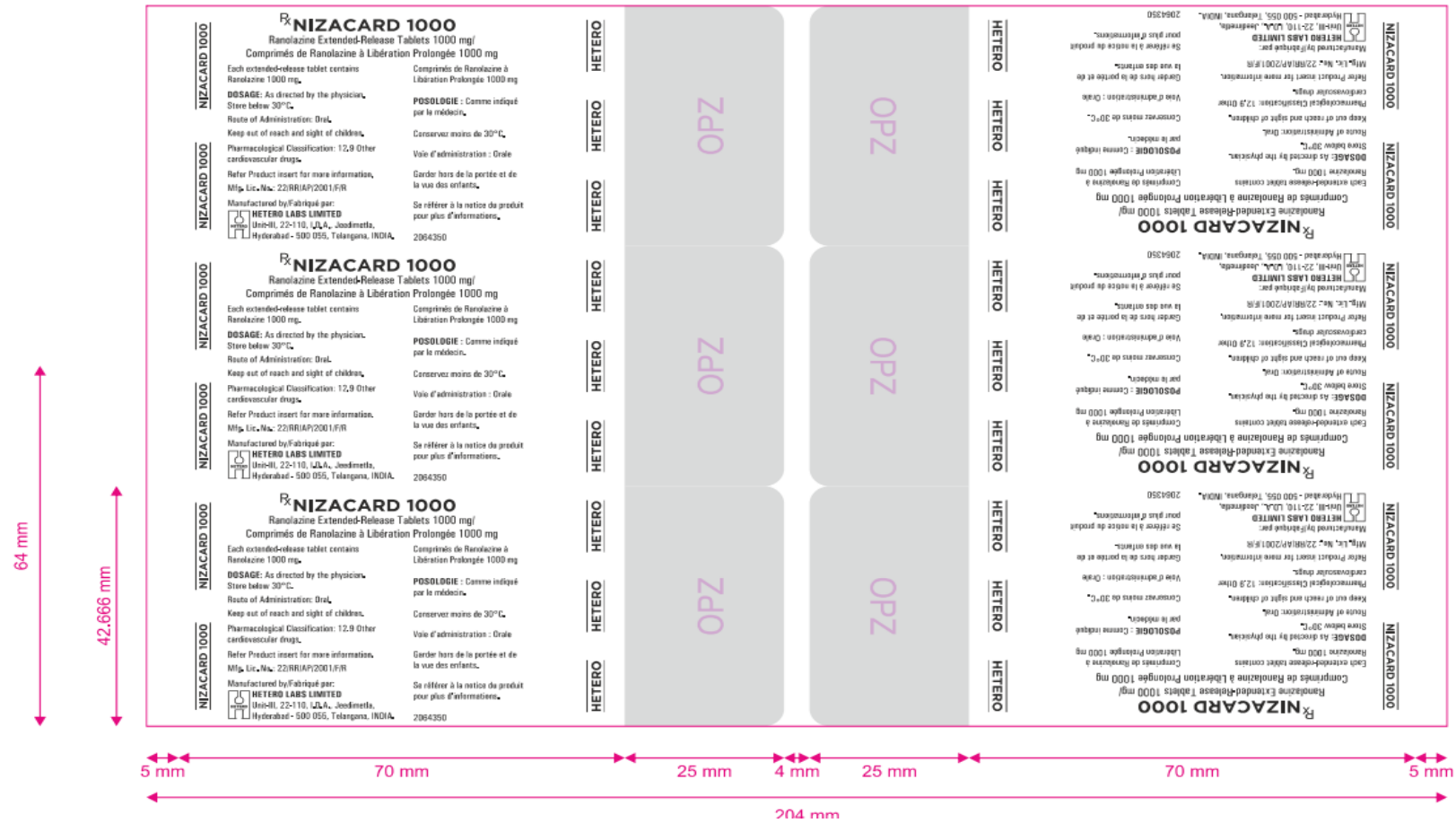
Application for renewal of registration was submitted on <DDMMYYYY>. The application was finalized in <number> rounds of evaluation. The product was confirmed to still be compliant to the standards of quality, safety and efficacy, hence registration was renewed on <DDMMYYYY>.

PART 5: CHANGE HISTORY

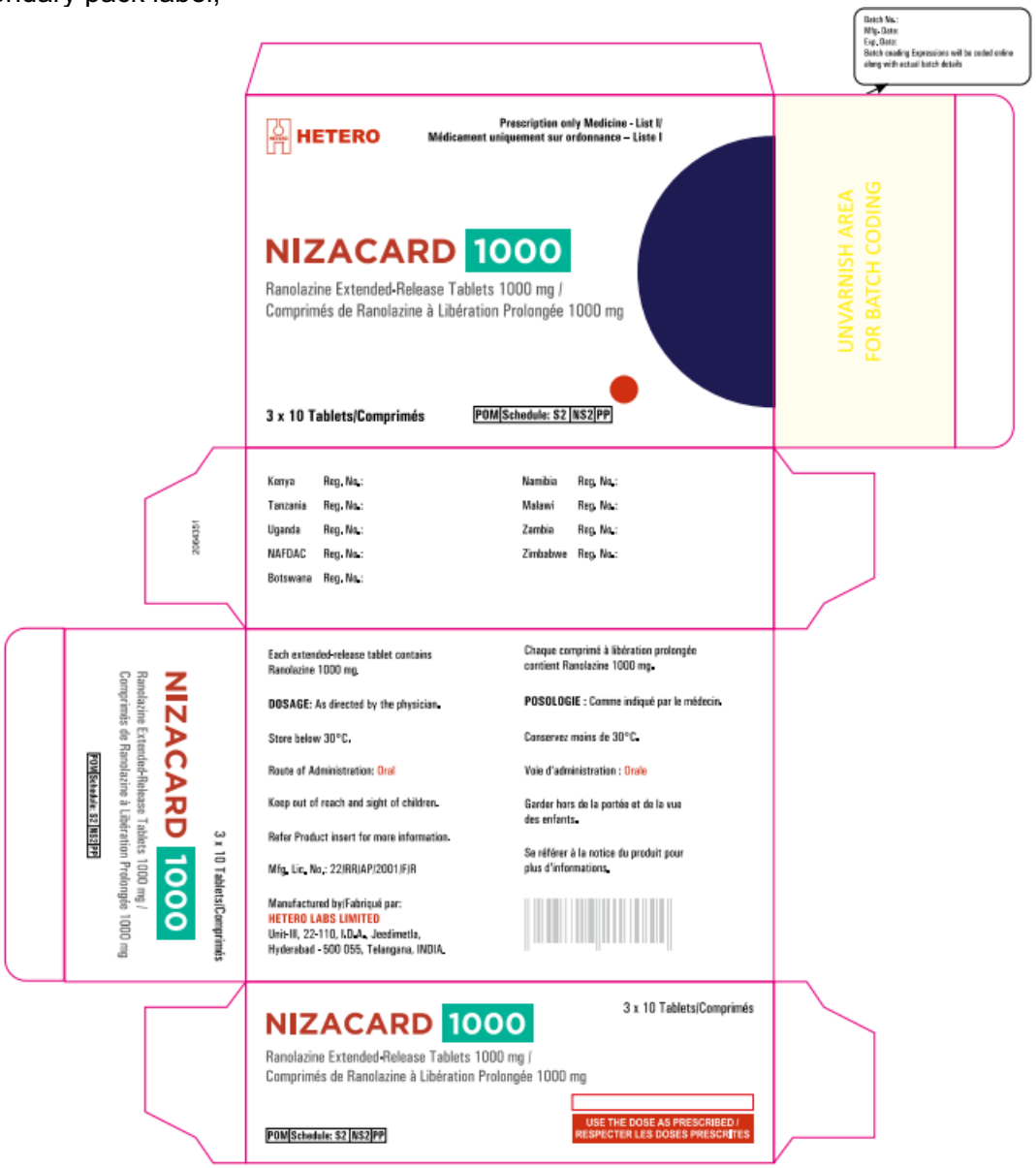
Version number	**Date**	**Description of update**	**Section(s) Modified**	**Approval date**

Annex I: Mock up labels;

Primary pack label;



Secondary pack label;



Effective date: 03/10/2022