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MINISTRYOFHEALTH

TANZANIA MEDICINES AND MEDICAL DEVICES AUTHORITY

PUBLIC ASSESSMENT REPORT FOR NICARDIA RETARD 20 (NIFEDIPINE 20 MG) EXTENDED-RELEASE TABLETS

Version number 01,

05/01/2023

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1. Introduction

Nicardia Retard 20 is a calcium antagonist of the 1,4-dihydropyridine type. Calcium antagonists reduce the transmembranal influx of calcium ions through the slow calcium channel into the cell. As a specific and potent calcium antagonist, nifedipine acts particularly on the cells of the myocardium and the smooth muscle cells of the coronary arteries and the peripheral resistance vessels. The main action of nifedipine is to relax arterial smooth muscle, both in the coronary and peripheral circulation. The Nicardia Retard 20 tablet is formulated to achieve controlled delivery of nifedipine in a release profile sufficient to enable once-daily administration to be effective in clinical use.

This application concerns a generic application claiming essential similarity with the innovator product Adalat LA 20 mg prolonged-release tablets, containing 20 mg nifedipine, which have been registered in the Netherlands by Bayer B.V. since 24 October 1991.

Nicardia Retard 20 is approved in Tanzania for the treatment of all grades of hypertension in adult and for the prophylaxis of chronic stable angina pectoris either as monotherapy or in combination with a beta-blocker.

1.1 Product details

Registration number	TAN 22 HM 0320
Brand name	Nicardia Retard 20
Generic name, strength and form	Nifedipine
ATC classification	ATC code: C08CA05 Selective calcium channel blockers with mainly vascular effect, dihydropyridine derivatives
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	Unique Pharmaceutical Laboratories (A Division of J.B Chemicals and Pharmaceutical Limited), Neelam Centre, ''B'' Wing, 4th Floor, Hind Cycle Road, Worli, Mumbai – 400 030, India
Local Technical	Unique Pharmaceutical Laboratories (A Division of J.B Chemicals and Pharmaceutical Limited),

Representative	Plot No.: 215-219, GIDC, Industrial Area, Panoli-394 116, Dist. Bharuch, India

1.2 Assessment procedure

The application for registration of Nicardia Retard 20 was submitted on 13/12/2019. The product underwent full assessment. Assessment was completed in three rounds of evaluation. Nicardia Retard 20 was registered on 04/08/2022.

1.3 Information for users

Visual description of the finished product	Orange coloured film coated biconvex round tablets with one side scored
Primary packing material	Alu – PVC blister of 10 x 10 tablets
Secondary packing materials	Carton box alongside with a package insert
Shelf-life and storage condition	36 months Do not store above 30°C, protect from light
Route of administration	Oral
Therapeutic indications	For the treatment of mild to moderate hypertension. For the management of chronic stable angina pectoris either as monotherapy or in combination with a beta-blocker

2. Labelling and product information

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 both full prescribing information as per SmPC and simplified information for patients.

Container labels

The product label information is presented in English. Details in the secondary pack label include:

Brand name: Nicardia Retard 20

Composition: Nifedipine

Pack size: 10 x 10’s tablets

Manufacturing details: batch number, manufacturing date, expiry date

Storage conditions: Do not store above 30°C, protect from light

Manufacturer address: Unique Pharmaceutical Laboratories (A Division of J.B Chemicals & Pharmaceutical Ltd), Plot No.: 215-219, GIDC, Industrial Area, Panoli-394

116, Dist. Bharuch, India.

Unique identifier: N/A
Special warnings/precautions or instructions for use: The product contains Lactose and Sunset Yellow FCF

The details of the primary pack include:
Brand name and strength: Nicardia Retard 20 mg extended-release tablets
Manufacturing details: batch number, manufacturing date, expiry date
Name of manufacturer: Unique Pharmaceutical Laboratories (A Division of J.B Chemicals & Pharmaceutical Ltd)

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)

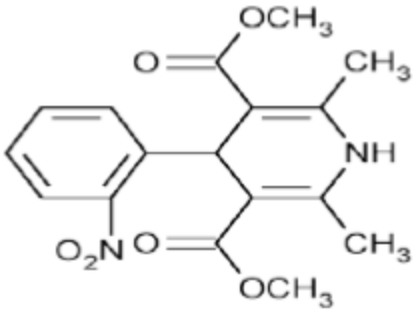
Information on quality of the API was submitted in form of full details.

General properties
Nifedipine API is compendia in USP and BP Pharmacopeia.

Molecular formula: $C_{17}H_{18}N_2O_6$

Chemical names:
3, 5 – Pyridinedicarboxylic acid, 1, 4 – dihydro– 2, 6 – dimethyl – 4 – (2 – nitrophenyl)- dimethyl ester

Structure:



Critical physico-chemical properties are:
Nifedipine is a yellow powder, freely soluble in acetone; practically insoluble in water. Nifedipine is classified as BCS class II molecule, therefore control of polymorphism and particle size is considered critical. The control of particle size distribution was demonstrated in the API specifications.

Manufacture

The API manufacturing site, Unique Chemicals (A Division of J. B. Chemicals & Pharmaceuticals Limited) Plot No. 5, Phase IV, GIDC Industrial Area, Panoli - 394 116, Dist-Bharuch, Gujarat, India was noted to comply with WHO GMP requirements as evidenced by the GMP certificate issued by Food and Drugs Control Administration, India. Nifedipine 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 USP standards and ICH guidelines. The parameters monitored during quality control are: description (visual), solubility, identification (IR, UV, HPLC), melting point, loss on drying, residue on ignition, perchloric acid titration, chloride & sulphate, assay (HPLC), related substances (HPLC), residual solvents (GC), clarity of solution and particle size distribution. Compliance to these specifications were established via batch analysis data and stability studies.

Stability and container closure system

Appropriate stability data have been provided supporting a suitable retest period of 60 months when stored in the proposed packaging.

Quality of the Finished Pharmaceutical Product

Formulation

Nicardia Retard 20 Nicardia Retard 20 is orange coloured film coated biconvex round tablets with one side scored

Nicardia Retard 20 mg extended-release tablets contains Nifedipine and other ingredients listed here after: Hypromellose, Microcrystalline Cellulose, Lactose Monohydrate, Dibasic calcium Phosphate Dihydrate, Corn starch, Purified water, Magnesium Stearate and Tabcoat TC Orange (Hypromellose, Titanium Dioxide, Macrogol, Talc, Sunset Yellow FCF and Aluminum Lake). 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 and Sunset Yellow FCF are of safety concern therefore appropriate warnings were included in the product label.

The development of the product has been described, the choice of excipients is justified and their functions explained. The active ingredient and excipients used are well known and of pharmacopoeial quality.

Manufacture

The finished product was manufactured at physical site. The compliance of the site to TMDA GMP standards was confirmed through site inspection on 15/08/2019

Specifications

The FPP is compendia in BP/USP pharmacopeial. The manufacturer controls the quality of the finished product as per USP and ICHQ3B requirements. The parameters monitored during quality control are: appearance, identity (HPLC, UV), average weight, uniformity of dosage units, loss on drying, dissolution, degradation products (HPLC), assay (HPLC) and microbial purity. Compliance to the standard was established using batch analysis data and stability data.

Stability and container closure system

Finished product stability studies have been conducted in accordance with current guidelines and in the packaging proposed for marketing. Based on available stability data, the proposed shelf-life of 36 months with storage recommendation “Do not store above 30°C, protect from light” is satisfactory.

Safety and efficacy information

Safety and efficacy of Nicardia Retard 20 was established through bioequivalence trial.

BE trial report number REP/BE/12/197, version 00 was submitted.

Study title	A randomized, single dose, open label, two-way, crossover Bioequivalence study of Nifedipine extended-release tablets 20 mg in healthy human subjects under fasting conditions	
Study design	Open label, single dose, randomized, two period, two treatments, two sequence, two-way crossover design.	
Study site	Raptim Research Ltd, A-226, M.I.D.C., T.T.C. Industrial Area, Mahape, Navi Mumbai-400 701, India	
Study dates	Initiated on 23rd November, 2013 Completed on 03rd December, 2013	
Primary objective	The objective of the study was to determine the bioequivalence of the Test product Nicardia Retard 20 (Nifedipine extended-release tablets USP 20 mg) manufactured by Unique Pharmaceutical and the reference listed drug Adalat Retard 20mg tablet manufactured by Bayer Schering Pharma AG, Germany	
Secondary objective	To monitor the adverse events and to ensure the safety of the subjects.	
Number of participants	24 healthy human subjects were enrolled	
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: ANU3018 Expiry date: September, 2016	Strength: 20 mg Batch number: BXG6KUI Expiry date: January, 2015
Analytical method	LC-MS/MS method was used for the determination of plasma concentration of analyte	
Statistical method	WinNonlin - Professional version 5.3	

Efficacy results are summarized as follows:
Ratio of mean and 90 % Confidence Interval (A Vs B) for Log Transformed data

Parameter	Geometric Least-Squares Means [1]		Test-to-Reference Ratio [2]	90% Classical Confidence Interval Limits [3]	
	Test (A)	Reference (B)		Lower	Upper
$Ln(C_{max})$	34.21	33.20	103.03	91.04	116.60
$Ln(AUC_{0-t})$	279.64	271.22	103.10	90.33	117.68
$Ln(AUC_{inf})$	368.08	344.81	106.75	93.34	122.08

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, Nicardia Retard 20 is equivalent and interchangeable with Adalat Retard 20mg tablet 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. Nicardia Retard 20 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 label