TANZANIA MEDICINES AND MEDICAL DEVICES AUTHORITY

PUBLIC ASSESSMENT REPORT FOR TURBOVAS-20 (20 MG ROSUVASTATIN (AS CALCIUM)) FILM COATED TABLETS

Version number 1.0

13 April, 2022

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1. Introduction

Turbovas-20 is a generic medicine of Crestor 20 mg film- coated tablets of Astra Zeneca is a blood cholesterol-lowering drug of statin family. Rosuvastatin is a selective and competitive inhibitor of HMG-CoA reductase, the rate-limiting enzyme that converts 3-hydroxy-3-methylglutaryl coenzyme A to mevalonate, a precursor for cholesterol. The primary site of action of Rosuvastatin is the liver, the target organ for cholesterol lowering. Rosuvastatin increases the number of hepatic LDL receptors on the cell-surface, enhancing uptake and catabolism of LDL and it inhibits the hepatic synthesis of VLDL, thereby reducing the total number of VLDL and LDL particles. Turbovas-20 is approved in Tanzania for use in adults, adolescents, and children aged 10 years or older.

1.1 Product details

Registration number	TAN 22 HM 0087
Brand name	Turbovas-20
Generic name, strength, and form	Each film coated tablet contains: Rosuvastatin Calcium Equivalent to Rosuvastatin 20 mg
ATC classification	ATC code: C10A A07- HMG-CoA reductase inhibitors
Distribution category	POM
Country of origin	India
Associated product	Turbovas-10 Film-Coated Tablets
Marketing Authorization Holder	Micro Labs Limited No.27, Race Course Road, Bangalore-560 001, Karnataka India
Local Technical Representative	Laborex Tanzania Limited Plot: 89-90 Alliance Auto House P.O. Box 70032, Dar es Salaam

1.2 Assessment procedure

The application for registration of Turbovas-20 was submitted on 11 July 2019. The product underwent full assessment. Assessment was completed in 3 (three) rounds of evaluation and the product was registered on 11 April 2022.

1.3 Information for users

Visual description of the finished product	Orange coloured, Circular biconvex film coated tablets with MICRO engraved on one side and other plain on another surface
Primary packing material	Alu/Alu blisters
Secondary packing materials	A printed carton box
Shelf-life and storage condition	36 months, do not store above 30°C. Store in the original package in order to protect from moisture
Route of administration	Oral
Therapeutic indications	Treatment of hypercholesterolaemia

	Adults, adolescents and children aged 10 years or older with primary hypercholesterolaemia (type IIa including heterozygous familial hypercholesterolaemia) or mixed dyslipidaemia (type IIb) as an adjunct to diet when response to diet and other non-pharmacological treatments (e.g. exercise, weight reduction) is inadequate. Adults, adolescents and children aged 10 years or older with homozygous familial hypercholesterolaemia as an adjunct to diet and other lipid lowering treatments (e.g. LDL apheresis) or if such treatments are not appropriate. Prevention of Cardiovascular Events Prevention of major cardiovascular events in patients who are estimated to have a high risk for a first cardiovascular event, as an adjunct to correction of other risk factors.

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: Turbovas-20

Composition: Rosuvastatin calcium equivalent to 20 mg Rosuvastatin

Pack size:3x 10 tablets

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

Storage conditions: Do not store above 30°C. Store in the original package in order to protect from moisture

Manufacturer address: physical address of release site

Unique identifier: Not applicable

Special warnings/precautions or instructions for use: Contains Lactose - See leaflet for further information

The details of the primary pack include:

Brand name and strength: Turbovas-20

Manufacturing details: batch number, manufacturing date and expiry date

Name of manufacturer: Micro 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 Ingredients

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

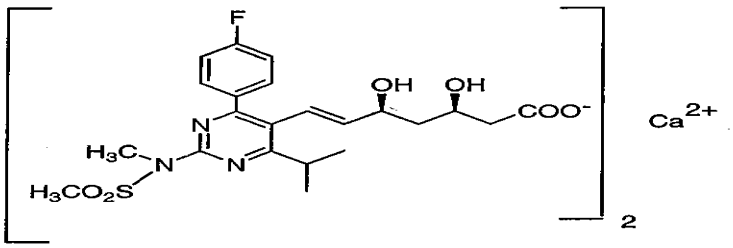
General Information

Rosuvastatin calcium API is compendia in USP and BP/Ph. Pharmacopeia.

Molecular formula: $C_{44}H_{54}F_2N_6O_{12}S_2.Ca$

Chemical name:
(3R,5S)-7-[4-(4-phlorophenyl)-6-isopropyl-2-[methyl(methylsulphonyl)amino]pirimidyn-5-yl]-3,5-dihydroxy-6(E)-heptenoicacid calcium salt (2:1)
Or
6-Heptanoic acid-7-[4-(4-phloropheny)-6-(1-methylethyl)-2-[methyl(methylsulphonyl)amino]-5-primidinyl]-3,5-dihydroxy-, calcium salt (2:1), (3R,5S,6E)
Or
Bis[(E)-7[4-(4-phlorophenyl)-6-isopropyl-2-methyl(methylsulphonyll)amino]pirimidyn-5-yl]-(3R,5S)-3,5-dihydroxyhept-6-enoic acid] calcium salt

Structure:



General properties

The active substance is a white to light yellow powder and is soluble in dimethylformamide, acetone and acetonitrile and is insoluble in water. It shows polymorphism. The molecule has 2 chiral centres; the manufacturer consistently produces the correct isomer and the same polymorphic form. Enantiomeric purity is controlled routinely by suitable analytical methods.

According to Biopharmaceutics Classification System (BCS), Rosuvastatin calcium is classified as Class 2 compound (low solubility, high permeability) hence particle size distribution (PSD) and polymorphism are considered critical parameters and form part of the API specifications.

Manufacture

Rosuvastatin calcium API manufacturer is Glenmark Pharmaceutical Limited, Plot No.43-45, KIADB, Plot No.3109, GIDC Industrial Estate, Ankleshwar-393002, Dist. Bharuch, Gujarat, India . The manufacturing complies with GMP requirements as evidenced by the GMP certificate issued by the Drug Control Administration Government of Gandhinagar, Gujarat State. Rosuvastatin calcium 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 Ph. Eur. standards and ICHQ3A. The parameters monitored during quality control are: appearance, solubility, identification, test for calcium, polymorphism, water content, enantiomeric purity, related substances, assay, residual solvents, particle size, and bulk density. Compliance to these specifications were established via batch analysis data and stability studies.

Stability and container closure system

The re-test period of Rosuvastatin calcium API is 48 months when packed in clear polyethylene bags under outer blank polyethylene bag. This bag is kept in triple laminated aluminium bag and placed in HDPE drum with storage condition ‘Keep the container tightly closed. It does not require any special storage conditions’.

Quality of the Finished Pharmaceutical Product

Formulation

Turbovas-20 is an orange coloured, circular biconvex film coated tablets with MICRO engraved on one side and other plain on another surface

Turbovas-20 contains the Rosuvastatin calcium and other ingredients listed here after: tribasic calcium phosphate, microcrystalline cellulose, lactose, crospovidone, magnesium stearate, titanium dioxide, sunset yellow. 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 manufacturer is Micro Labs Limited, Micro labs limited No. 92, SIPCOT, Hosur-635 126, Tamil nadu, India. The compliance of the site to TMDA GMP standards was confirmed through site inspection on 07-08 December, 2016.

Specifications

The FPP is compendia in BP and USP. The manufacturer controls the quality of the finished product as per in-house standards and ICH requirements. The parameters monitored during quality control are: Appearance, Identification of API and colour agents, Average and uniformity of weight, Water content, Uniformity of Dosage units, Disintegration time, Dissolution, Related substances, Assay, Microbial enumeration tests, and Test for specified Microorganisms. Compliance to the standard was established using batch analysis data and stability data.

Stability and container closure system

Stability studies were conducted on a 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 Aluminium/Aluminium blisters with storage condition 'Do not store above 30°C. Store in the original package in order to protect from moisture'.

Safety and efficacy information

Safety and efficacy of Turbovas-20 was established through a bioequivalence trial.

BE trial report number PRT-004-14 was submitted.

Study title	A bioequivalence study of randomized, open label, single oral dose, two-way crossover design with two-period, two treatment and two sequence of Rosuvastatin Tablets 20 mg relative to Crestor (Rosuvastatin 20 mg Tablets) in healthy Thai volunteers under fasting conditions
Study design	An open label, randomized, two-treatment, two-period, two-sequence, single dose, crossover, comparative bioequivalence study in healthy adult human male subjects under fasting conditions
Study site	Institution, Clinical facility and Analytical Laboratory Bio-innova and Synchron Co, Ltd 9/11-14 SoiWattana, Sukhumvit 19 Road Klongtoeynua, Wattana, Bangkok 10110 Thailand. Clinical Laboratory Professional Laboratory Management Corp Co, Ltd. 49761 SoiLadprio 101, Klongchun, Bangkapi, Bangkok 10240 Thailand.
Study dates	19 April 2015 to 08 July 2015

Primary objective	To compare the rate and extent of absorption of a generic formulation with that of a reference formulation when given as equal labelled dose	
Secondary objective	To evaluate the safety of both test and reference formulation	
Number of participants	Planned: 33 subjects Enrolled: 33 subjects Dosed: 33 subjects Withdrawn – 00 subjects Completed: 33 subjects, Bio-sample analyzed: 33 subjects Pharmacokinetic and statistical data analyzed: 33 subjects	
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: RUDG001 Expiry date: 08/2015	Strength: 20 mg Batch number: KN254 Expiry date: 12/2016
Analytical method	LC-MS/MS method was used for the determination of plasma concentration of analyte	
Statistical method	SAS® software Version	

Efficacy results are summarized as follows:

Parameter	Test	Reference	90 % Confidence interval	DF	CV (%)
AUC0-t (ng.hr/mL)	193.33±85.06	197.09±79.72	90.57-1104.77	31	
AUC0-inf (ng.hr/mL)	202.76±85.92	205.66±81.10	89.34-104.54	31	
Cmax (ng/mL)	24.32±9.70	24.54±9.95	90.73-108.12	31	

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, Turbovas-20 tablets manufactured by Micro Labs Limited is equivalent and interchangeable with Crestor (Rosuvastatin 20 mg Tablets) manufactured by IPR Pharmaceuticals Inc. Canovanas, Puerto Rico, USA 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. Turbovas-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

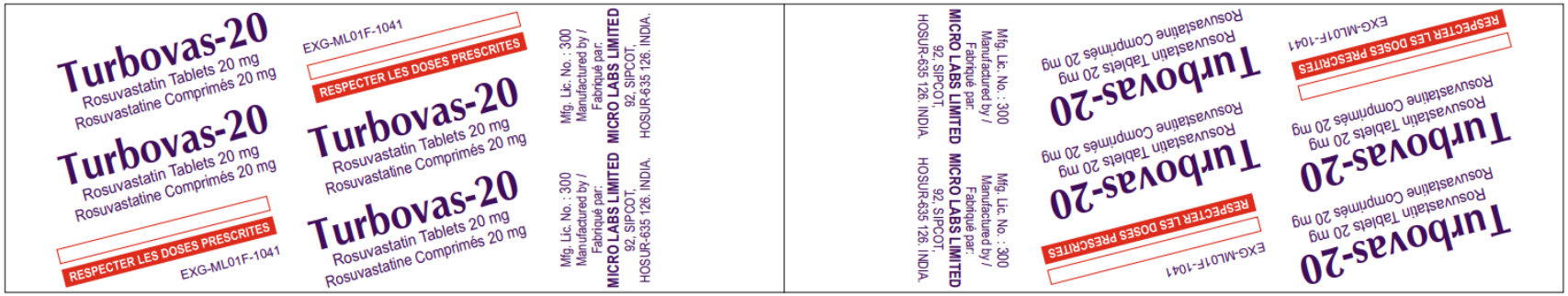
NA

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;