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MINISTRYOFHEALTH

TANZANIAMEDICINES ANDMEDICALDEVICESAUTHORITY

PUBLIC ASSESSMENT REPORT FOR ATORVAS 20 (ATORVASTATIN CALCIUM 20 MG) FILM COATED TABLETS

Version number 1
3rd January, 2023

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1. Introduction

ATORVAS 20 is a generic medicine of Lipitor (Atorvastatin calcium 20 mg). ATORVAS 20 is a Lipid modifying agents medicine belonging to HMG-CoA-reductase inhibitors group. ATORVAS 20 is a selective, competitive inhibitor of HMG-CoA reductase, the rate-limiting enzyme responsible for the conversion of 3-hydroxy-3-methyl-glutaryl-coenzyme A to mevalonate, a precursor of sterols, including cholesterol. Triglycerides and cholesterol in the liver are incorporated into very low-density lipoproteins (VLDL) and released into the plasma for delivery to peripheral tissues. Low-density lipoprotein (LDL) is formed from VLDL and is catabolised primarily through the receptor with high affinity to LDL (LDL receptor). Atorvastatin lowers plasma cholesterol and lipoprotein serum concentrations by inhibiting HMG-CoA reductase and subsequently cholesterol biosynthesis in the liver and increases the number of hepatic LDL receptors on the cell surface for enhanced uptake and catabolism of LDL. Atorvastatin reduces LDL production and the number of LDL particles. Atorvastatin produces a profound and sustained increase in LDL receptor activity coupled with a beneficial change in the quality of circulating LDL particles. Atorvastatin is effective in reducing LDL-C in patients with homozygous familial hypercholesterolaemia, a population that has not usually responded to lipid-lowering medicinal products

ATORVAS 20 is approved in Tanzania for use in adults, adolescents and children aged 10 years or older with primary hypercholesterolaemia including familial hypercholesterolaemia

1.1 Product details

Registration number	TAN 21 HM 0105
Brand name	ATORVAS 20
Generic name, strength and form	Atorvastatin calcium 20 mg
ATC classification	C10AA05**,** Lipid modifying agents, HMG-CoA-reductase inhibitors
Distribution category	POM
Country of origin	India
Associated product	ATORVAS 10 (Atorvastatin calcium 10 mg)
Marketing Authorization Holder	Sunberg Life Sciences PVT. Limited, No.15, Gopalakrishna Road, T. Nagar, Chennai 600 017. Tamil Nadu. India Telephone: +91 44 2345 2030-34 Telefax: +91 44 2345 2036, E-Mail: vijay@softgelhealthcare.com
Local Technical Representative	Moraf Pharmaceuticals Ltd, P.O. Box 21323, Dar es Salaam,

	Tanzania.

1.2 Assessment procedure

The application for registration of ATORVAS 20 was submitted on 22nd November, 2017. The product underwent full assessment. Assessment was completed in five rounds of evaluation. ATORVAS 20 was registered on 29th March, 2022.

1.3 Information for users

Visual description of the finished product	Orange coloured circular slightly biconvexed film coated tablets and scored in the middle on one side
Primary packing material	3 × 10's Alu - Alu Blister Pack
Secondary packing materials	Carton box
Shelf-life and storage condition	24 months Store below 30°C. Protect from light and moisture
Route of administration	Oral
Therapeutic indications	Atorvastatin is indicated as an adjunct to diet for reduction of elevated total cholesterol (total-C), LDL-cholesterol (LDL-C), apolipoprotein B, and triglycerides in adults, adolescents and children aged 10 years or older with primary hypercholesterolaemia including familial hypercholesterolaemia (heterozygous variant) or combined (mixed) hyperlipidaemia (corresponding to Types IIa and IIb of the Fredrickson classification) when response to diet and other no pharmacological measures is inadequate. Atorvastatin is also indicated to reduce Total-C and LDL-C in adults with homozygous familial hypercholesterolaemia as an adjunct to other lipid-lowering treatments (e.g. LDL apheresis) or if such treatments are unavailable. Prevention of cardiovascular disease Prevention of cardiovascular events in adult patients 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 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: ATORVAS 20 (Atorvastatin calcium 20 mg) film coated tablets

Composition: Atorvastatin calcium 20 mg, Lactose, Microcrystalline Cellulose, Povidone K30, Calcium Carbonate, Croscarmellose Sodium, Magnesium Stearate, Opadry White, Sunset Yellow Lake, Dichloromethane, Isopropyl Alcohol

Pack size: 3 × 10's

Manufacturing details: <batch number, manufacturing date, expiry date>

Storage conditions: Store below 30°C. Protect from light and moisture

Manufacturer address: The Madras Pharmaceuticals, No.137B, Old Mahabalipuram Road, Karapakkam, Chennai - 600 096, Tamil Nadu, 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: ATORVAS 20 (Atorvastatin calcium 20 mg) film coated tablets

Manufacturing details: <batch number, manufacturing date, expiry date>

Name of manufacturer: The Madras Pharmaceuticals

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

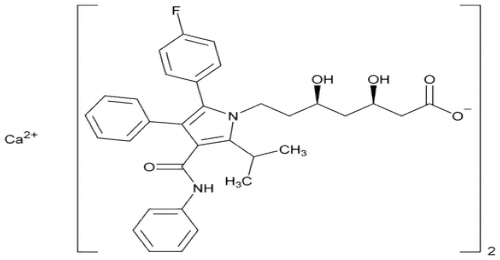
General properties

Atorvastatin Calcium API is compendia in USP/BP/JP

Molecular formula: $C_{66}H_{68}CaF_2N_4O_{10}.3H_2O$

Chemical name: (3R, 5R)-7-[2-(4-fluoropheilyl)-3-phellyl-4- (phenylcarbamoyl)-5-(propan-2-yl)-lH-pyrrol-lylJ-3, 5 dihydroxyheptanoate calcium Trihydrate

Structure:



Critical physico-chemical properties of the API were very slightly soluble in water. acetonitrile; slightly soluble in ethanol (95 percent), freely soluble in methanol.

Manufacture

The API manufacturing site, DSM Sinochem Pharmaceuticals India Private Limited, Bhai Mohan Singh Nagar, Toansa, Tehsil: Balachaur; District: Nawanshahr - 144 533 Punjab, India was noted to comply with WHO GMP requirements as evidenced by the GMP certificate issued by Food and Drug Authority, Punjab, Pariwar Kalyan Bhawan, Sector 34-A Chandigarh. Atorvastatin 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 in-house standards and ICHQ3A. The parameters monitored during quality control are: Appearance, solubility, identification,

optical rotation, related substances, heavy metal, water, assay, particle size distribution. Compliance to these specifications were established via batch analysis data and stability studies.

Stability and container closure system

The re-test period of Atorvastatin Calcium API is 48 months when packed in LDPE bag which in turn placed in HDPE drum and stored at 30ºC.

Quality of the Finished Pharmaceutical Product

Formulation

ATORVAS 20 is an Orange colored circular slightly biconvex film coated tablet with a scored in the middle on one side packed in Alu - Alu Blister. ATORVAS 20 contains < Atorvastatin calcium and other ingredients listed here after Lactose, Microcrystalline Cellulose, Povidone K30, Calcium Carbonate, Croscarmellose Sodium, Magnesium Stearate, Opadry White, Sunset Yellow Lake, Dichloromethane, Isopropyl Alcohol. 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 is of safety concern therefore appropriate warnings were included in the product label.

Manufacture

The finished product was manufactured at The Madras Pharmaceuticals, No.137B, Old Mahabalipuram Road, Karapakkam, Chennai 600 096. India. The compliance of the site to TMDA GMP standards was confirmed through site inspection on 5th June 2014.

Specifications

The FPP is compendia in BP/USP. The manufacturer controls the quality of the finished product as per in-house and ICHQ3B requirements. The parameters monitored during quality control are: Appearance, identification, average weight, uniformity of weight, disintegration time, dissolution, uniformity of content, related substance, assay, microbial limit test, residual solvents. 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°C ± 2°C/75% ± 5%RH for 24 months and 40°C ± 2°C/75% ± 5%RH for 6 months. Based on the stability data presented, the approved shelf-life is 24 months when stored in Alu – Alu blisters at below 30°C.

Safety and efficacy information

Safety and efficacy of ATORVAS 20 was established through bioequivalence trial
BE trial report number 18/16/368 was submitted.
In case of BE:

Study title	An randomized, open label, two treatment, two period, two sequence, single dose crossover comparative, oral bioavailability study between Atorvas 20 mg" manufactured by Madras Pharmaceuticals is bioequivalent to the reference product "Lipitor 20 mg tablet" manufactured by Pfizer
Study design	An randomized, open label, two treatment, two period, two sequence, single dose crossover comparative, oral bioavailability study
Study site	**Clinical study site** Taab Biostudy Services, 69, Ibrahimpur Road, Jadavpur, Kolkata-700032 **Clinical Laboratories** Clinical Pharmacological unit Taab Biostudy Services, 77/2/1B/1 Baderaipur road, 1st floor, Jadavpur, Kolkata-700032 **Analytical Laboratories** Taab Biostudy Services 76/D, Ibrahimpur Road, Kolkata-700032 **Company performing pharmacokinetic/statistical analysis** Taab Biostudy Services 76/D, Ibrahimpur Road, Kolkata-700032
Study dates	Start and stop dates for each phase of the clinical study: Phase-I: 12.04.2017 to 29.04.2017 Period-II: 17.04.2017 to 01.05.2017 Dosing dates: Dosed date in Period-I: 13.04.2017 Dosed date in Period-II: 30.04.2017

	Dates of Blood Sample Collection: Period I: 13.04.2017 Period II: 30.04.2017 Plasma Analysis Start date: 04/05/2017 End date: 11/05/2017	
Primary objective	To compare the bioequivalence and characterize the pharmacokinetic profile of the sponsor's Atorvas 20 relative to that of reference product "Lipitor 20 mg tablet" manufactured by Pfizer in healthy, adult, human male subjects under fasting conditions and to assess the bioequivalence	
Secondary objective	To monitor the safety of the subjects	
Number of participants	40 healthy adult human male subjects	
Monitored parameters	Cmax, AUC, Tmax, Half-life	
Investigational medicinal products	Test Product	Reference product
	Strength: 20 mg Batch number: R1516 Expiry date: 03/2018	Strength: 20 mg Batch number: J17646 Expiry date: 06/2017
Analytical method	LC-MS/MS	
Statistical method	SAS Version 9.1.3/WinNonlin (Version 5.3) (Pharsight Corporation, USA)	

Efficacy results are summarized as follows:

Parameter	Test	Reference	% Ratio of geometric means	90 % Confidence interval	DF	CV (%)
AUC0-t (ng.hr/mL)	4.67	4.94	94.56	92.19-98.21	38	40
AUC0-inf (ng.hr/mL)	4.72	5.06	93.37	91.04-96.96	38	41
Cmax (ng/mL)	2.38	2.44	97.43	94.74-102.64	38	25

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, ATORVAS 20 is equivalent and interchangeable with Lipitor 20 mg 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. ATORVAS 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

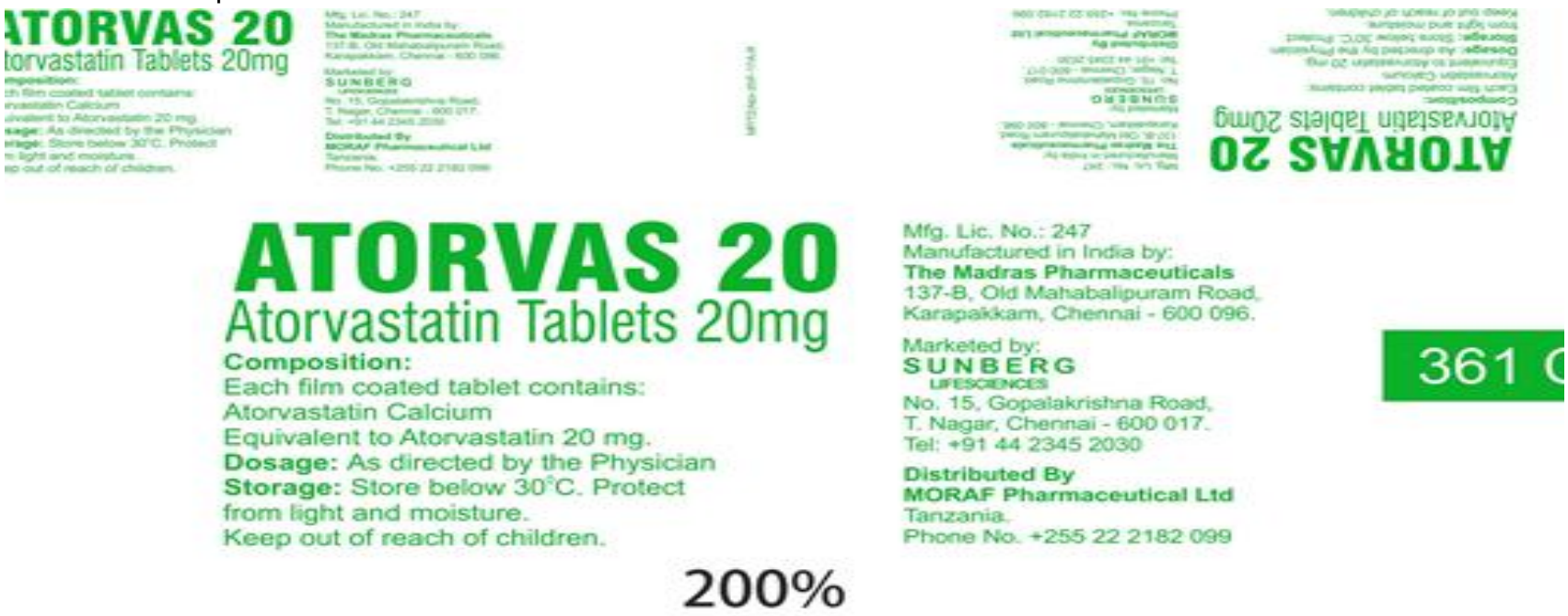
Re-registration applications

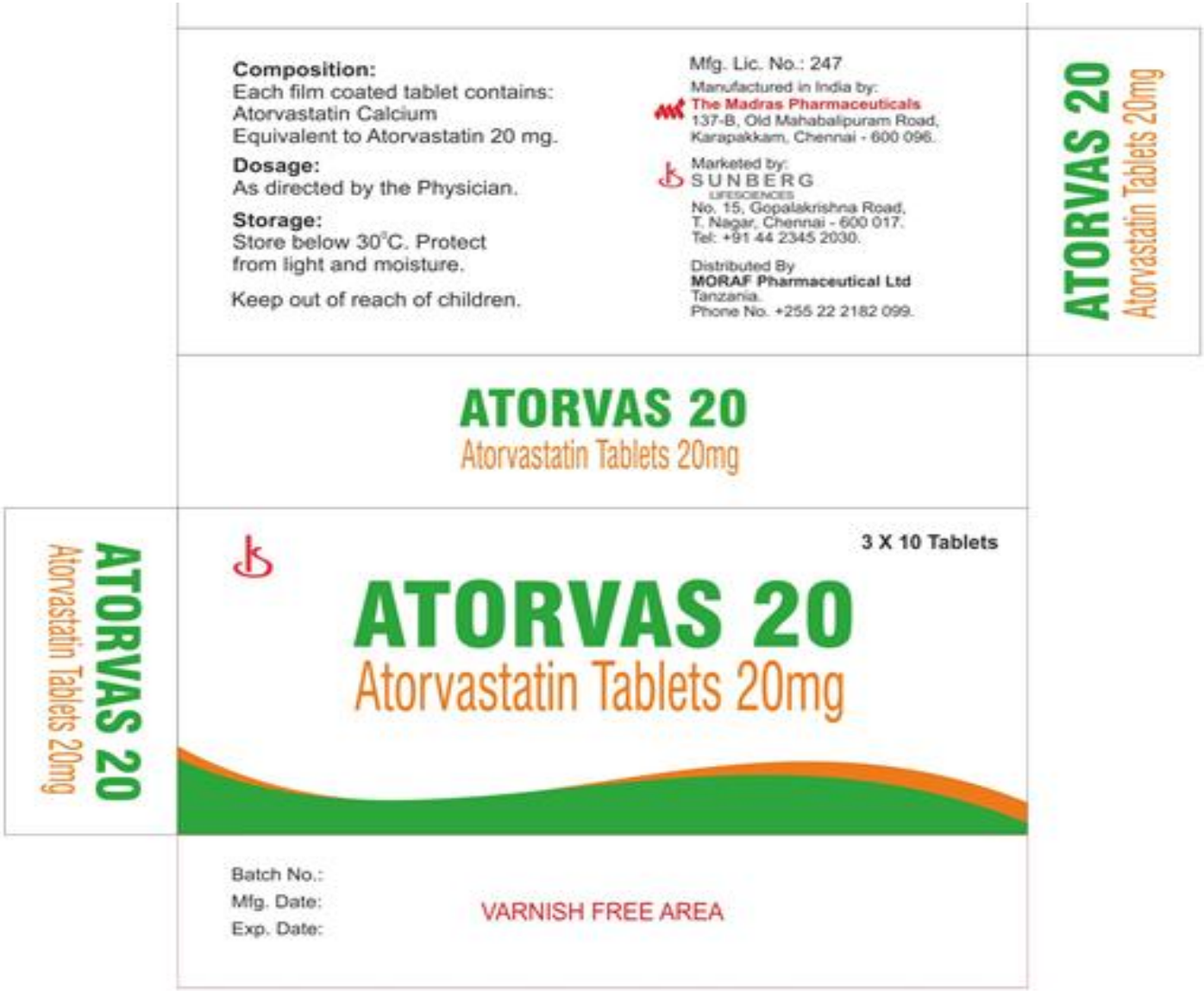
NA

PART 5: CHANGE HISTORY

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

Annex I: Mock up label




Composition:
Each film coated tablet contains:
Atorvastatin Calcium
Equivalent to Atorvastatin 20 mg.
Dosage:
As directed by the Physician.
Storage:
Store below 30°C. Protect
from light and moisture.
Keep out of reach of children.
Mfg. Lic. No.: 247
Manufactured in India by:
The Madras Pharmaceuticals
137-B, Old Mahabalipuram Road,
Karapakkam, Chennai - 600 096.
Marketed by:
SUNBERG
LIFESCIENCES
No. 15, Gopalakrishna Road,
T. Nagar, Chennai - 600 017.
Tel: +91 44 2345 2030.
Distributed By
MORAF Pharmaceutical Ltd
Tanzania.
Phone No. +255 22 2182 099.
ATORVAS 20
Atorvastatin Tablets 20mg
ATORVAS 20
Atorvastatin Tablets 20mg
ATORVAS 20
Atorvastatin Tablets 20mg
3 X 10 Tablets
ATORVAS 20
Atorvastatin Tablets 20mg
Batch No.:
Mfg. Date:
Exp. Date:
VARNISH FREE AREA