THE UNITED REPUBLIC OF TANZANIA

MINISTRY OF HEALTH

TANZANIA MEDICINES AND MEDICAL DEVICES AUTHORITY

PUBLIC ASSESSMENT REPORT FOR AURITZ 20 (ROSUVASTATIN CALCIUM EQUIVALENT TO ROSUVASTATIN 20 MG) FILM- COATED TABLETS

Version number 01, 06/01/2023

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1. Introduction

Auritz 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.

Auritz 20 is approved in Tanzania for treatment of Treatment of hypercholesterolaemia in adults, adolescents and children aged 6 or older with primary hypercholesterolaemia and prevention of cardiovascular events.

1.1 Product details

Registration number	TAN 22 HM 0413
Brand name	Auritz 20
Generic name, strength and form	Each film-coated tablet contains 20 mg of rosuvastatin as 20.8 mg of rosuvastatin calcium
ATC classification	HMG-CoA reductase inhibitors ATC code: C10A A07
Distribution category	POM
Country of origin	India
Associated product	The finished product is presented as a film-coated tablet containing 10 mg & 20 mg of rosuvastatin calcium as active substance
Marketing Authorization Holder	Mega Lifesciences Public Company Limited. 384 Soi 6, Pattana 3 Road,Bangpoo Industrial Estate, Mood 4,Praeksa,Muang, Samutprakarn, Samutprakarm 10280 Thailand
Local Technical Representative	Mega Wecare Tanzania Limited, P.O.BOX 1899, Nyerere Road,10 Vingunguti Dar es Salaam

1.2 Assessment procedure

The application for registration of Auritz 20 was submitted on 22/11/2021. The product underwent full assessment. Assessment was completed in one round of evaluation. Auritz 20 was registered on 21/09/2022.

1.3 Information for users

Visual description of the finished product	Pink round, biconvex coated tablets, debossed “063” on one side and plain on other side
Primary packing material	Pack of 3 x 10’s tablets in Alu-Alu pack
Secondary packing materials	Carton box alongside with a package insert
Shelf-life and storage condition	24 months Store below 30°C, Protect from light and moisture
Route of administration	Oral
Therapeutic indications	Auritz 20 are indicated for treatment Primary hypercholesterolaemia (type IIa including heterozygous familial hypercholesterolaemia) or mixed dyslipidaemia (type IIb) as an adjunct to diet when response to diet and other nonpharmacological treatments (e.g. exercise, weight reduction) is inadequate. Homozygous familial hypercholesterolaemia as an adjunct to diet and other lipid lowering treatments (e.g. LDL apheresis) or if such treatments are not appropriate

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 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: Auritz 20

Composition: Each film-coated tablet contains 20 mg of rosuvastatin as 20.8 mg of rosuvastatin calcium
Pack size: 3 x 10's tablets
Manufacturing details: batch number, manufacturing date, expiry date
Storage conditions: Store below 30°C in its own pack
Manufacturer address: Inventia Healthcare Limited F1-F1/1-F75/1, Additional Ambernath M.I.D.C. Ambernath (East), Thane 421 506, Maharashtra state, India

Unique identifier: N/A
Special warnings/precautions or instructions for use: This medicinal product contains lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

The details of the primary pack include:
Brand name and strength: Auritz 20
Manufacturing details: batch number, manufacturing date, expiry date
Name of manufacturer: Inventia Healthcare Limited F1-F1/1-F75/1, Additional Ambernath M.I.D.C. Ambernath (East), Thane 421 506, Maharashtra state, India

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)

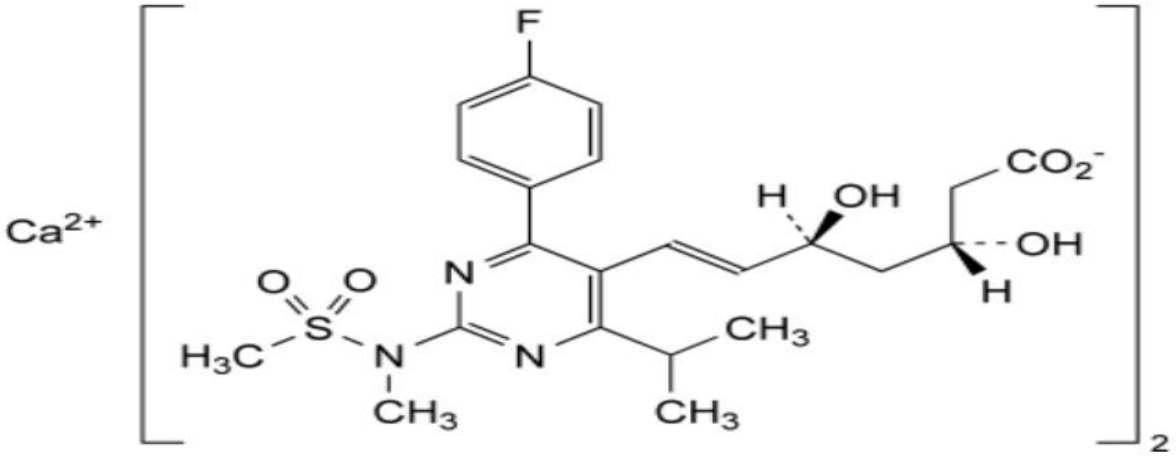
Information on quality of the API was submitted in form of full details.

<u>General properties</u>
Rosuvastatin calcium API is compendia in USP and BP/Ph. Pharmacopeia.

Molecular formula: $C_{44}H_{54}CaF_2N_6O_{12}S_2$

Chemical names:
Calcium bis[(3R,5S,6E)-7-[4-(4-fluorophenyl)-6-(1-methylethyl)-2-[methyl(methylsulfonyl)amino]pyrimidin-5-yl]-3,5-dihydroxyhept-6-enoate].

Structure:



Critical physico-chemical properties are:

The active substance rosuvastatin calcium is an established active substance described in the European Pharmacopoeia (Ph.Eur.)/USP. The active substance is a white to almost white powder. It is freely soluble in methylene chloride, slightly soluble in water and practically insoluble in anhydrous ethanol. Rosuvastatin calcium is an optically active molecule, having two stereogenic centres and hence 4 possible stereoisomers. The substance used is the 3R,5S isomer. The amorphous form is produced.

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

The API manufacturing sites, Hetero Drugs Limited; Unit-IX, Plot No.1, Hetero Infrastructure SEZ Ltd, N. Narasapuram (Village), Nakkapalli (Mandal), Visakhapatnam District-531 081, Andhra Pradesh, India and Dr. Reddy's Laboratories Limited, Chemical Technical Operations, Unit-V Peddadevulapalli, Tripuraram Mandal Nalgonda District, Telangana, India – 508 207, India were noted to comply with WHO GMP requirements as evidenced by the GMP certificates issued by ←----------->. 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 USP standards and ICH guidelines. The parameters monitored during quality control are: Appearance, solubility, Identification (IR), chemical test for Calcium, Water (by KF), Assay (HPLC), Enantiomeric purity (HPLC), related substances (HPLC), polymorphic, particle size distribution and residual solvents. Compliance to these specifications were established via batch analysis data and stability studies.

Stability and container closure system

The stability results indicate that the active substance manufactured by the proposed supplier is stable and justify the proposed retest period of 60 months when stored in the proposed container.

Quality of the Finished Pharmaceutical Product

Formulation

Auritz 20 is presented as pink, round, biconvex, coated tablet debossed “063” on one side and plain on other side.

Auritz 20 contains Microcrystalline Cellulose PH-122 NF, Lactose Monohydrate (SD250) NF, Carboxymethyl cellulose Calcium NF, Magnesium stearate NF, Opadry Pink 03K54121 IH, Purified water USP/Ph. Eur. 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.

Film coat: Composition of Opadry Pink 03K54121 IH; Hypromellose, Titanium Dioxide, Triacetin and Red Iron Oxide

Manufacture

The finished product was manufactured at Inventia Healthcare Limited F1-F1/1-F75/1, Additional Ambernath M.I.D.C. Ambernath (East), Thane 421 506, Maharashtra state, India. The compliance of the site to TMDA GMP standards was confirmed through physical inspection on 25/01/2019

Specifications

The FPP is compendia in EP/USP. The manufacturer controls the quality of the finished product as per USP standards and ICH requirements. The parameters monitored during quality control are: appearance, identity (HPLC and UV spectrum and coloring agents), average mass and Uniformity of mass, Dissolution (By HPLC), 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

Stability studies were conducted on three (3) batches of the finished product stored at 30 ± 2°C & 75% ± 5% RH for 24 months and 40 ± 2°C & 75% ± 5% RH for 6 months. Based on available stability data, the proposed shelf-life of 24 months is acceptable.

Safety and efficacy information

Safety and efficacy of Auritz 20 was established through bioequivalence trial
BE trial report number 641/13 was submitted.

Study title	An open label, balanced, randomized, two-treatment, two-period, two sequence, single dose, crossover, oral bioequivalence study of Rosuvastatin Calcium 40 mg tablets of Inventia Healthcare Private Limited comparing with that of CRESTOR® (rosuvastatin calcium) 40 mg tablets of AstraZeneca Pharmaceuticals LP Wilmington, DE 19850 in healthy, adult, human subjects under fasting conditions	
Study design	An open label, balanced, randomized, two-treatment, two-period, two-sequence, single dose, crossover	
Study site	QPS Bioserve India Pvt. Limited, # 6-56/6/1A, Opp. IDPL Factory, Balanagar, Hyderabad – 500 037, Andhra Pradesh, India	
Study dates	Clinical (Period I & II); 22/03/2014- 12/04/2014 Bioanalytical: 22/04/2014 - 02/05/2014	
Primary objective	To assess the bioequivalence of Rosuvastatin Calcium 40 mg tablets of Inventia Healthcare Private Limited comparing with that of CRESTOR® (rosuvastatin calcium) 40 mg tablets of AstraZeneca Pharmaceuticals LP Wilmington, DE 19850 in healthy, adult, human subjects under fasting conditions	
Secondary objective	To monitor adverse events and ensure the safety of subjects.	
Number of participants	A total of 52 normal, healthy human subjects were enrolled in the study	
Monitored parameters	Tmax, Cmax, AUC0→t, AUC0→∞, AUC% Extrapolation Kel and T1/2	
Investigational medicinal products	Test Product	Reference product
	Strength: 40 mg Batch number: EXB/910/01 Expiry date: December,	Strength: 40 mg Batch number: BK0059 Expiry date: 04/30/16

	2015	
Analytical method	LC-MS/MS method was used for the determination of plasma concentration of analyte	
Statistical method	GLM of SAS® Version 9.1.3 (SAS Institute Inc., USA)	

Efficacy results are summarized as follows

Parameters	Geometric mean		% Ratio	90 % CI for log transformed data				DF
	Test	Reference	T/R	Lower	Upper	Power	Intra CV	
LAUCinf	405.2619	426.6585	94.99	89.27	101.06	100.0	19.0	<.0001
LAUCt	386.3257	408.3374	94.61	88.69	100.93	100.0	19.8	<.0001
LCmax	52.0652	53.7121	96.93	88.63	106.01	99.2	27.7	<.0001

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, Auritz 40 is equivalent and interchangeable with Crestor 40 mg film coated tablets AstraZeneca Pharmaceuticals LP Wilmington under acceptable in vivo experimental conditions.

The Bio-equivalence study was carried out on Auritz 40. Based on acceptable Bioequivalence study for Auritz 40, a bio-waiver is requested for Auritz 20.

The biowaiver was approved based on additional strength. In relation to the strength biowaiver, comparative dissolution studies have been provided for Auritz 20 strength and the Auritz 40 bio batch in pH 1.2, pH 4.5 acetate buffer and pH 6.8 phosphate buffer. The study demonstrated similarity of the dissolution profiles and thus from this point of view the biowaiver has been accepted.

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 Auritz 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

Primary artwork

Secondary artwork


21.0 mm
3 mm
3 mm
12 mm
64.0 mm
3 mm
Rx Prescription Drug
AURITZ 20
Rosuvastatin Tablets USP 20 mg
MEGA
We care
3 x 10 Tablets
AURITZ 20
Rosuvastatin Tablets USP 20 mg
3 x 10 Tablets
Space For Pharma Code 7 x 20 mm
2.5 mm
2.5 mm
Rx Prescription Drug
AURITZ 20
Rosuvastatin Tablets USP 20 mg
MEGA
We care
3 x 10 Tablets
3 mm
2.5 mm
2.5 mm
AURITZ 20
Rosuvastatin Tablets USP 20 mg
3 x 10 Tablets
Space For Pharma Code 7 x 20 mm
12 mm
AURITZ 20
Rosuvastatin Tablets USP 20 mg
Each film coated tablet contains:
Rosuvastatin Calcium USP
equivalent to Rosuvastatin ..... 20 mg
Product specifications: USP
Indication, Dosage, Contraindication, Side effects (see enclosed leaflet)
• Keep out of reach of children
• Protect from light and moisture
• Store below 30°C in a dry place
Read the instructions carefully before use.
Do not exceed prescribed dose
Mfg. Lic. No. : KD/638
This medicine contains lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.
Manufactured for :
MEGA LIFESCIENCES (AUSTRALIA) PTY LTD
Victoria 3810, Australia.
Manufactured by :
INVENTIA HEALTHCARE LIMITED
F1-F1/1-F75/1, Additional Ambernath M.I.D.C.,
Ambernath (East), Thane 421506, Maharashtra State, India.
MEGA
We care
xxxxxxxxx
Artwork Code No.
3 mm
TZ Reg. No. :
Unvarnished area
for batch details & 2D Barcode
65 x 20 mm
3 mm
3 mm