THE UNITED REPUBLIC OF TANZANIA

MINISTRY OF HEALTH

TANZANIA MEDICINES AND MEDICAL DEVICES AUTHORITY

PUBLIC ASSESSMENT REPORT FOR ULTROX (ROSUVASTATIN CALCIUM EQUIVALENT TO ROSUVASTATIN 10 MG) FILM- COATED TABLETS

Version number 01, 06/01/2023

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1. Introduction

Ultrox 10 mg film-coated tablet is a generic medicine of Crestor 10 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.

Ultrox 10 mg film-coated tablet 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 0499
Brand name	Ultrox 10 mg film-coated tablets
Generic name, strength and form	Each tablet contains 10 mg rosuvastatin (as 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 of rosuvastatin calcium as active substance
Marketing Authorization Holder	Nobel Ilaç Sanayii Ve Ticaret A.S. Umraniye, 34768 Istanbul, Turkey
Local Technical Representative	Kas Medics Limited Umoja Complex, Plot No, 11, First Floor, Uf09 & Uf10, Vingunguti Industrial Area, long Nyerere Road Adjacent To 10 West Commercial Complex, P. O. Box 7856, Dar es Salaam

Effective date: 03/10/2022

1.2 Assessment procedure

The application for registration of Ultrox 10 mg film-coated tablets was submitted on 17/06/2021. The product underwent full assessment. Assessment was completed in three rounds of evaluation. Ultrox 10 mg film-coated tablets was registered on 21/09/2022.

1.3 Information for users

Visual description of the finished product	Pink colored, round, biconvex unnotched film coated tablets
Primary packing material	Pack of 2 x 14'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 in its own pack
Route of administration	Oral
Therapeutic indications	Ultrox 10 mg film-coated tablets 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: Ultrox 10 mg film-coated tablets

Composition: Each tablet contains 10 mg rosuvastatin (as rosuvastatin calcium)

Pack size: 2 x 14's tablets

Manufacturing details: batch number, manufacturing date, expiry date

Storage conditions: Store below 30°C in its own pack

Manufacturer address: NOBEL ILAÇ SANAYII VE TICARET A.S, Sancaklar Mah. Eski Akçakoca Cad. No: 29981100 DÜZCE / TÜRKİYE

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: Ultrox 10 mg film-coated tablets

Manufacturing details: batch number, manufacturing date, expiry date

Name of manufacturer: NOBEL ILAÇ SANAYII VE TICARET A.S, Sancaklar Mah. Eski Akçakoca Cad. No: 29981100 DÜZCE / TÜRKİYE.

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 CEP procedure.

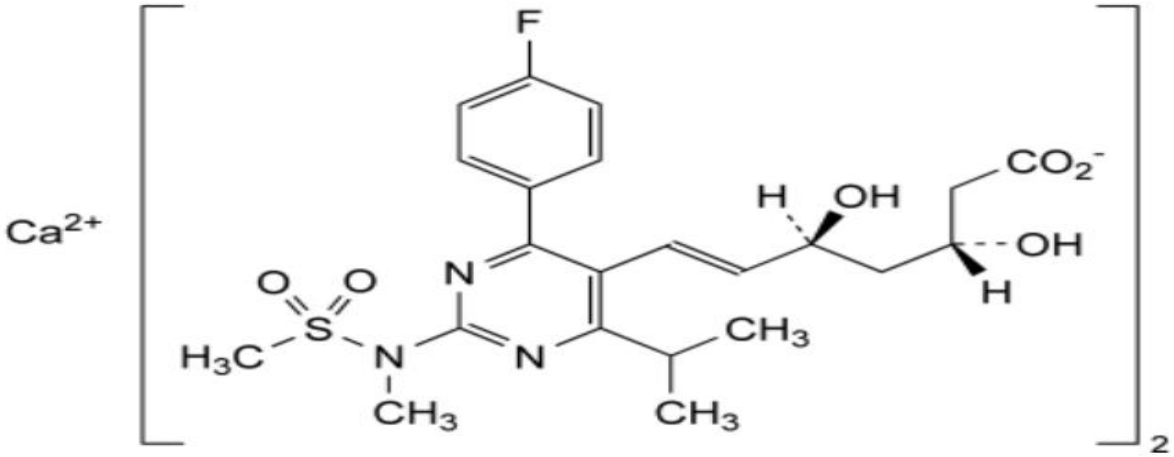
General properties

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

Two different manufacturers (MSN Laboratories Pvt. Ltd, Sy. No. 317, 320, 321, 322, 323, 604 & 605 Rudraram (Village), Patancheru (Mandal), Sangareddy District, Pin code: 502 329, Telangana, India and Changzhou Pharmaceutical Factory Nantong Chanyoo Pharmatech Co., Ltd, No.2 Tonghai Si Road, Yangkou Chemical Industrial Park, Rudong Coastal Economic Development Zone, China-226 407 Nantong, Jiangsu Province). For both manufacturers, the CEP procedure was used for the active substance. CEPs have been submitted; therefore, no details on the manufacturing process have been included. The manufacturing facilities were noted to comply with WHO GMP requirements as evidenced by the GMP certificates issued by Drugs control Administration Government of Telangana and PEOPLE'S REPUBLIC OF CHINA

(JIANGSU) FOOD AND DRUG ADMINISTRATION respectively. 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 European Pharmacopoeia (Ph.Eur.) 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 active substance is stable for 24 months when stored under the stated conditions. Assessment thereof was part of granting the CEP and has been granted by the EDQM

Quality of the Finished Pharmaceutical Product

Formulation

Ultrox 20 mg film-coated tablets is presented as pink colored, round, biconvex unnotched film coated tablets.

Ultrox 20 mg film-coated tablets contains Lactose monohydrate, Calcium carbonate, Microcrystalline cellulose PH 102, Crospovidone CL (Kollidon CL), Hydroxypropyl cellulose-SSL (HPC-SSL), Magnesium stearate and Purified water. The quantities of all ingredients are confirmed to be in line with the recommendations of Handbook of Pharmaceutical Excipients, Edition 8th 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 KB Low viscosity White 310A180023; Macragol (PEG) Polyvinyl alcohol graft copolymer, Copolyvidone, Titanium dioxide, Kaolin & Sodium lauryl sulphate

Composition of Opadry KB Low viscosity Orange 310A130010; Macragol (PEG) Polyvinyl alcohol graft copolymer, Copolyvidone, Titanium dioxide, Kaolin, Sodium lauryl sulphate & FD&C Yellow #6/ sunset yellow FCF aluminum lake

Composition of Opadry KB Low Viscosity Red 310A150019; Macragol (PEG) Polyvinyl alcohol graft copolymer, Copolyvidone, Titanium dioxide, Kaolin, Sodium lauryl sulphate & Carmine

Composition of Kollicoat Protect; Polyvinyl alcohol-polyethylene glycol graft copolymer, Polyvinyl alcohol & Silicon dioxide

Manufacture

The finished product was manufactured at NOBEL İLAÇ SANAYİİ VE TİCARET A.Ş, Sancaklar Mah. Eski Akçakoca Cad. No:299 81100 Düzce Türkiye. The compliance of the site to TMDA GMP standards was confirmed through desk review on 21/06/2021

Specifications

The FPP is compendia in EP/USP. The manufacturer controls the quality of the finished product as per EP 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, Hardness, Disintegration time, Enantiomeric Purity, water content, 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

The Bio-equivalence study was carried out on Ultrox 20 mg film-coated tablets. Based on acceptable Bioequivalence study for Ultrox 20 mg film-coated tablets, a bio-waiver is requested for Ultrox 10 mg film-coated tablets.

The biowaiver was approved based on additional strength. In relation to the strength biowaiver, comparative dissolution studies have been provided for Ultrox 10 mg film-coated tablets strength and the Ultrox 20 mg film-coated tablets bio batch in 0.1N hydrochloric acid, 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 Ultrox 10 mg film-coated 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

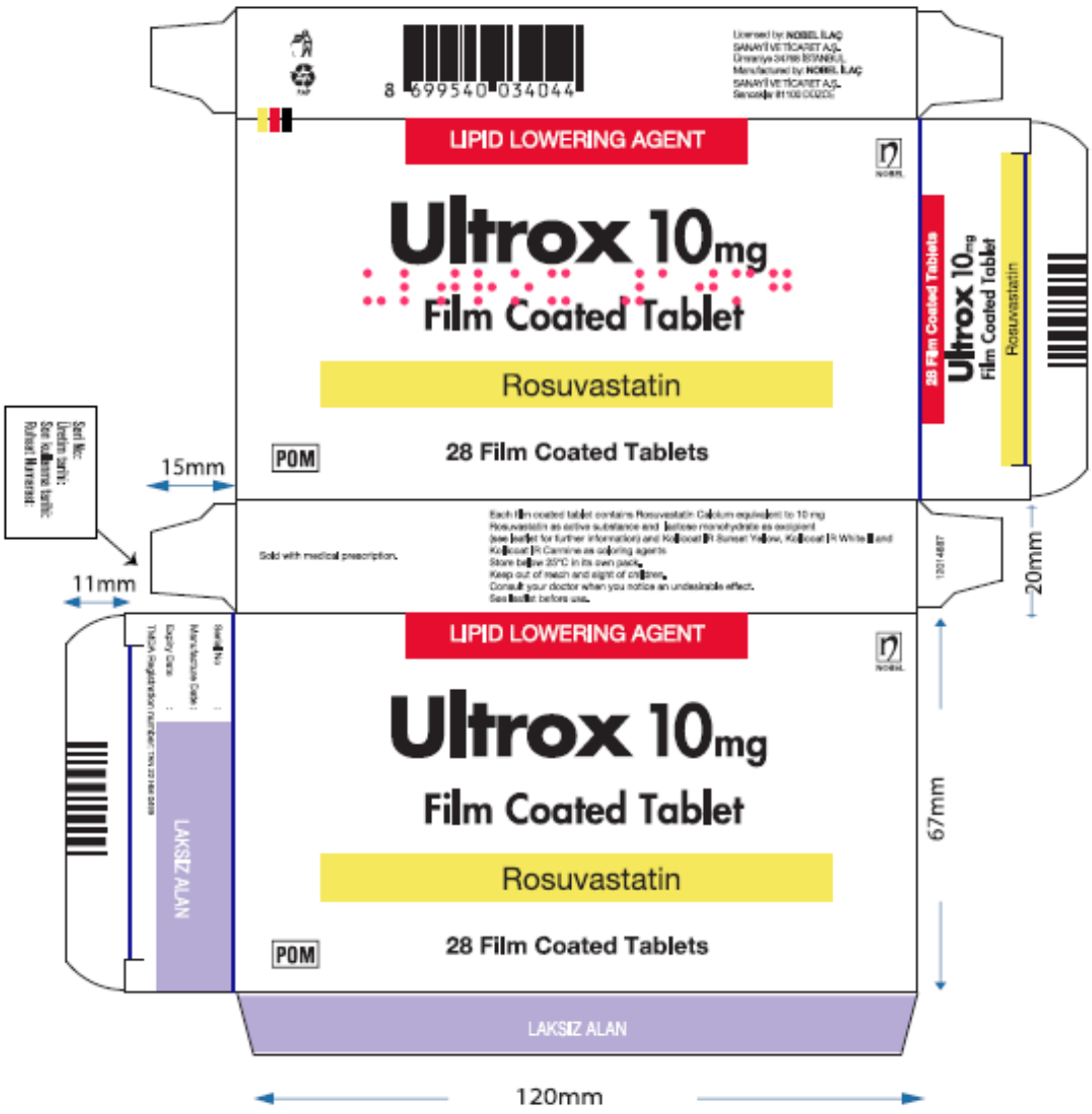
Re-registration applications

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 label



ULTROX 10 MG 28 FİLM TABLET KUTU KAS TANZANYA			
Pantone 185 C Pantone 106 C Siyah	KOMBİ	LAKSIZ ALAN	