THE UNITED REPUBLIC OF TANZANIA

MINISTRY OF HEALTH

TANZANIA MEDICINES AND MEDICAL DEVICES AUTHORITY

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

Version number 01, 06/01/2023

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1. Introduction

Ultrox 20 mg film-coated tablet 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.

Ultrox 20 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 0386
Brand name	Ultrox 20 mg film-coated tablets
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 20 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

1.2.Assessment procedure

The application for registration of *Ultrox 20 mg film-coated tablets* was submitted on *17/06/2021*. The product underwent *full assessment*. Assessment was completed in three rounds of evaluation. *Ultrox 20 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 20 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 20 mg film-coated tablets*

Composition: *Each film-coated tablet contains 20 mg of rosuvastatin as 20.8 mg of 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: 299 81100 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 20 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: 299 81100 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)

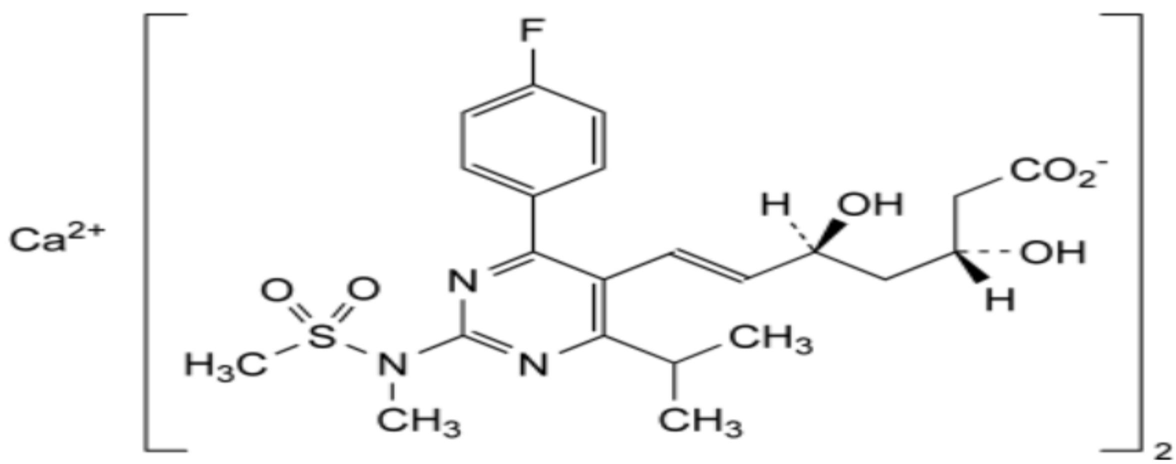
Information on quality of the API was submitted in form of *CEP procedure.*

<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[(3*R*,5*S*,6*E*)-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 coating:

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

Safety and efficacy of *Ultrox 20 mg film-coated tablets* was established through *bioequivalence trial.*
BE trial report number *117B11, Final Version:* 26.01.2012 was submitted.

Study title	*Comparative bioavailability study of Rosuvastatin after single dose administration (fasting conditions) of Rosuvastatin 20 mg Film-coated Tablets (Nobel Ilac, Turkey) and Crestor 20 mg Filmtabletten (AstraZeneca GmbH, Germany) in 42 healthy subjects*
Study design	*Single dose, randomised, open label, two-treatment, two-period, two-sequence crossover, at one study site*
Study site	*Clinical study site:* *Farmagen IKU Merkezi* *Gaziantep Universitesi Teknopark* *Burc Yolu Sahinbey* *TR-27000 Gaziantep, Turkey* *Bioanalytical study site:* *ACC GmbH Analytical Clinical Concepts* *Schöntalweg 9* *D-63849 Leidersbach, Germany*
Study dates	*Study initiation date (Preliminary screening of first subject); 30 Sept, 2011* *Study Completion date; 17 Oct, 2011 (final examination of last subject)*
Primary objective	*To determine the bioavailability of the test product and the reference product containing 20 mg rosuvastatin after single dose administration under fasting conditions in healthy subjects*
Secondary objective	*To evaluate the safety of both test and reference formulation*
Number of participants	*A total of 42 normal, healthy human subjects were enrolled in the study*
Monitored parameters	*Primary parameters:* C_{max} and $AUC_{(0-t)}$ *Secondary parameters:* $AUC_{(0-\infty)}$, $AUC_{t(last)-\infty}$, T_{max}, $T_{1/2}$ and λ_z

Investigational medicinal products	Test Product Rosuvastatin 20 mg Film-coated Tablets	Reference product Crestor 20 mg Filmtabletten
	Strength: *20 mg* Batch number: *0LR0001A* Expiry date: *April 2012*	Strength: *20 mg* Batch number: *LM1099A4* Expiry date: *November 2012*
Analytical method	*LC-MS/MS method was used for the determination of plasma concentration of analyte*	
Statistical method	*SAS (SAS Software Release 9.2, Copyright© by SAS Institute Inc., Cary, NC, USA*	

Bioequivalence results are summarized as follows:
Mean (arithmetic mean) plasma concentration-time curves of rosuvastatin after administration of the test product and the reference product (N = 42)

Relative bioavailability and pharmacokinetic parameters

Test (N = 42)						
Variable	**Geom. mean**	**Arithm. mean**	**SD**	**CV**	**Range**	**Median**
$AUC_{(0-t)}$	92.218	108.464	59.3849	54.8	287.045 - 18.638	94.328
C_{max}	9.947	12.007	7.3461	61.2	34.013 - 1.603	9.464
t_{max}	4.1	4.3	0.94	22.1	5.5 - 1.0	4.5
Reference (N = 42)						
Variable	**Geom. mean**	**Arithm. mean**	**SD**	**CV**	**Range**	**Median**
$AUC_{(0-t)}$	93.179	104.299	44.7115	42.9	218.016 - 13.639	106.221
C_{max}	10.414	11.916	5.7189	48.0	27.084 - 1.249	10.831
t_{max}	4.0	4.2	0.96	22.8	5.5 - 1.0	4.5

Calculated 90 %-confidence intervals, geometric mean ratios and CV_{res} (%) from the OLS analysis of rosuvastatin (N = 42)

Parameter	**LCL (%)**	**Ratio (%)**	**UCL (%)**	**CV_{res} (%)**
$AUC_{(0-t)}$	91.09	98.97	107.53	22.87
$AUC_{(0-\infty)}$	92.87	100.49	108.73	21.70
C_{max}	86.03	95.52	106.06	29.07

LCL = lower 90 %-confidence limit
UCL = upper 90 %-confidence limit

According to calculated 90 %-confidence intervals; the acceptance limits of 80.00% – 125.00% are met by the $AUC_{(0-t)}$ and C_{max} values. Furthermore, the safety profile of the test product is similar to that of reference product. Therefore, *Ultrox 20 mg film-coated tablets* is equivalent and interchangeable with *Crestor 20 mg Filmtabletten (AstraZeneca GmbH, Germany)* 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 *Ultrox 20 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	**Date**	**Description of update**	**Section(s) Modified**	**Approval date**

Annex I: Mock up label

ULTROX 20 MG 28 FİLM TABLET KUTU KAS TANZANYA			83x140x20 mm
Pantone 185 Pantone 326 Siyah	Kombi	Laksız alan / lac free area	Kabartma / emboss