THE UNITED REPUBLIC OF TANZANIA

MINISTRY OF HEALTH

TANZANIA MEDICINES AND MEDICAL DEVICES AUTHORITY

PUBLIC ASSESSMENT REPORT FOR CREVASTIN 20 (ROSUVASTATIN CALCIUM EQUİVALENT TO ROSUVASTATIN 20 MG) FILM COATED TABLETS

Version number 1

05 January, 2022

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1. Introduction

CREVASTIN 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. CREVASTIN 20 is approved in Tanzania for use in adults, adolescents, and children patients aged 10 years or older.

1.1 Product details

Registration number	TAN 22 HM 0021
Brand name	CREVASTIN 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	Turkey
Associated product	CREVASTIN 10 Film-Coated Tablets
Marketing Authorization Holder	Bilim İlaç San. ve Tic. A.Ş. Kaptanpaşa mah. Zincirlikuyu Cad. No: 184 34440 Beyoğlu, İstanbul Country: Turkey E-Mail: info@bilimilac.com.tr
Local Technical Representative	Tridem Pharma Tanzania Limited P.O. box 23145, Plot No 70, Keko Mwanga Dar es salaam -Tanzania E-Mail: bensonaloyce@guilinpharma.com

1.2 Assessment procedure

The application for registration of CREVASTIN 20 was submitted on 28 January 2020. The product underwent full assessment. Assessment was completed in 2 (two) rounds of evaluation and the product was registered on 10 January 2022.

1.3 Information for users

Visual description of the finished product	Pink-pinkish coloured, one side is written “20”, round, biconvex film coated tablet
Primary packing material	Alu/Alu blisters
Secondary packing materials	A printed carton box
Shelf-life and storage condition	24 months, Store below 30°C, at room temperature.
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 (see section 5.1), 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: CREVASTIN 20

Composition: 20.80 mg Rosuvastatin calcium equivalent to 20 mg Rosuvastatin

Pack size:28 tablets

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

Storage conditions: Store below 30°C, at room temperature.

Manufacturer address: physical address of release site

Unique identifier: Not applicable

Special warnings/precautions or instructions for use: Read enclosed patient information leaflet before use. In case of an unexpected side effect, consult your physician.

The details of the primary pack include:

Brand name and strength: CREVASTIN 20 (20 mg)

Manufacturing details: batch number, manufacturing date and expiry date

Name of manufacturer: Bilim İlaç

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.

Site No.1: MSN LABORATORIES LIMITED

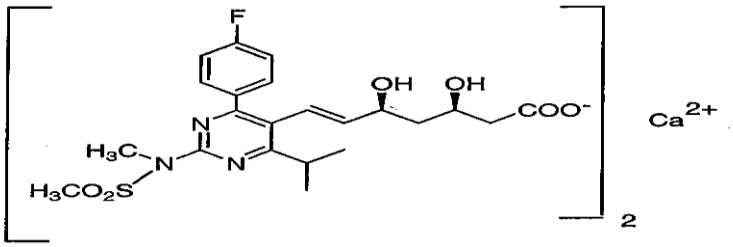
General Information

Rosuvastatin calcium API is compendia.

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 MSN LABORATORIES LIMITED, Sy.No. 317 & 323, Rudraram (V), Patancheru (Mandal), Medak District, Pin code: 502 329., Andhra Pradesh, India . The manufacturing complies with GMP requirements as evidenced by the GMP certificate issued by the Drugs Control Administration Government of Andhra Pradesh-India. 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 (IR and HPLC), test for calcium, Polymorphism (XRPD), water content, Enantiomeric purity, Related substances (HPLC), Assay (By HPLC), Residual solvents (GC), Particle size, and microbiological purity. 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 36 months when packed in Low-Density Polyethylene (LDPE) bag with storage condition 'Do not store above 25^{o}C. Protect from light and moisture'.

Site No.2: Nosch Labs Pvt. Ltd

General Information

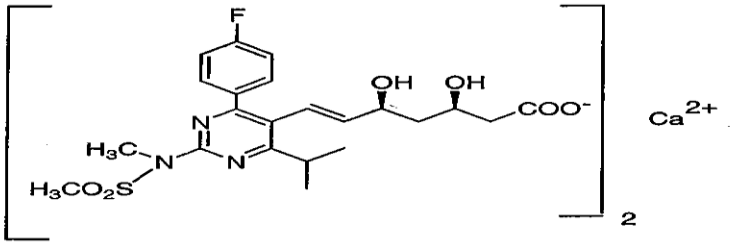
Rosuvastatin calcium API is compendia.

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 hygroscopic 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) is considered critical parameter and form part of the API specifications.

Manufacture

Rosuvastatin calcium API manufacturer is Nosch Labs Pvt. Ltd, Unit-II, Survey No.14, Gaddapotharam (Village), IDA, Kazipally, Jinnaram Mandal, Medak District, Telangana – 502 319, INDIA. The manufacturing complies with GMP requirements as evidenced by the GMP certificate issued by the Dug Control Administration Hyderabad -India. 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 (IR and HPLC), test for calcium, water content, Enantiomeric purity, Related substances (HPLC), Assay (By HPLC), Residual solvents (GC), Particle size, and microbiological purity. 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 Low-Density Polyethylene (LDPE) bag with storage condition 'Do not store above 25^{o}C. Protect from light and moisture'.

Quality of the Finished Pharmaceutical Product

Formulation

CREVASTIN 20 is a pink-pinkish coloured, one side is written "20", round, biconvex film coated tablet

CREVASTIN 20 contains the Rosuvastatin calcium and other ingredients listed here after: Lactose monohydrate, Microcrystalline cellulose, Disodium phosphate dihydrate, Crospovidone, Magnesium stearate, Macrogol (PEG), Talc, Polyvinyl alcohol, Titanium dioxide, Red iron oxide, Yellow iron oxide. 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 Bilim İlaç San. ve Tic. A.Ş., Gebze Organize Sanayi Bölgesi 1900 Sokak No:1904 41480 Gebze-Kocaeli, Turkey. The compliance of the site to TMDA GMP standards was confirmed through desk-review on 25 June, 2021.

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, Weight of tablet, Weight variation, 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 24 months and 40± 2°C & RH: 75% ± 5% RH for 6 months. Based on the stability data presented, the approved shelf-life is 24 months when stored in Aluminium/Aluminium blisters with storage condition 'Store below 30°C, at room temperature'.

Safety and efficacy information

The biowaiver was approved based on additional strength.

CREVASTIN 20 fulfilled the criteria for waiving an in-vivo bioequivalence study as per relevant TMDA guidance. Dissolution profiles of CREVASTIN 20 (Rosuvastatin 20 mg) Tablets of Bilim İlaç San.ve Tic. A.Ş., was compared Rosuvastatin 40 mg Tablets of Bilim İlaç San.ve Tic. A.Ş..

Less than 85% of the labelled amount of Rosuvastatin had dissolved in 15 minutes in all three media. Therefore, necessitating calculation of similarity factor f2, which was noted to be above 50.

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. CREVASTIN 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

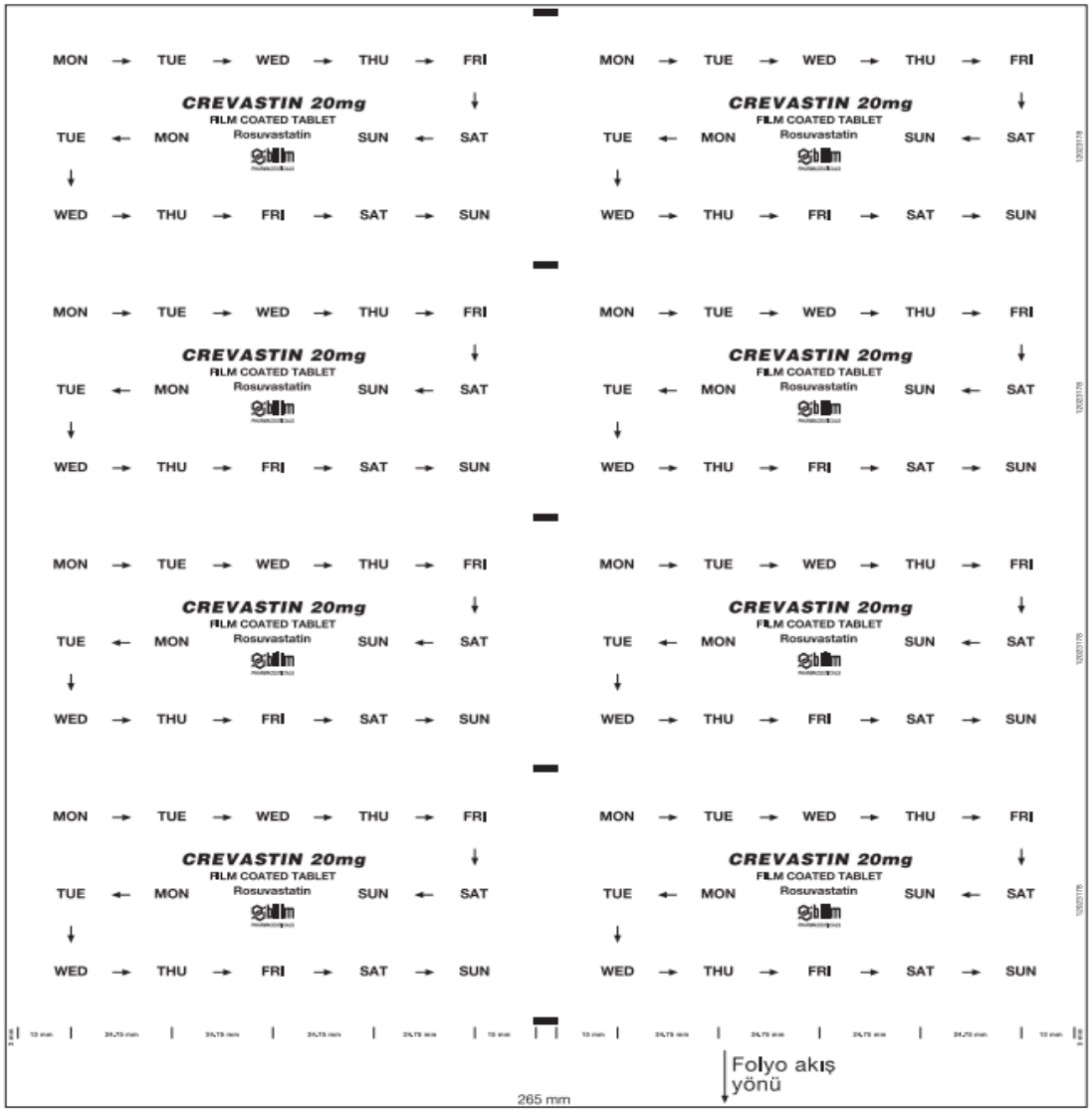
Application for renewal of registration was submitted on <DDMMYYYY>. The application was finalized in <number> rounds of evaluation. The product was confirmed to still be compliant to the standards of quality, safety and efficacy, hence registration was renewed on <DDMMYYYY>.

PART 5: CHANGE HISTORY

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

Annex I: Mock up labels;

Primary pack label;



Effective date: 03/10/2022

Secondary pack label;

Effective date: 03/10/2022