European Directorate for the Quality of Medicines & HealthCare | Direction européenne de la qualité du médicament & soins de santé
COUNCIL OF EUROPE
CONSEIL DE L'EUROPE

Certification of Substances Department

Certificate of suitability
No. R0-CEP 2018-112-Rev 00

Name of the substance:
ROSUVASTATIN CALCIUM

Name of holder:
SHREEGEN PHARMA LIMITED
Flat No. 405, DasaiahPlaza
Moosapet, Kukatpally
India-500018 Hyderabad , Telangana

Site(s) of production:
SEE ANNEX 1

After examination of the information provided on the manufacturing method and subsequent processes (including purification) for this substance on the site(s) of production listed in annex, we certify that the quality of the substance is suitably controlled by the current version of the monograph **ROSUVASTATIN CALCIUM** no. 2631 of the European Pharmacopoeia, current edition including supplements, only if it is supplemented by the test(s) mentioned below, based on the analytical procedure(s) given in annex.

– Test for residual solvents by gas chromatography (Annex 2)

Methanol	not more than 3000 ppm
Toluene	not more than 890 ppm
tert-Butylmethyl ether	not more than 5000 ppm

In the last steps of the synthesis water is used as solvent.

A risk management summary for elemental impurities has been provided. (Annex 3)

The re-test period of the substance is 18 months if stored in double polyethylene bags (outer black), placed in a polyethylene container.

The holder of the certificate has declared the absence of use of material of human or animal origin in the manufacture of the substance.

The submitted dossier must be updated after any significant change that may alter the quality, safety or efficacy of the substance.

Manufacture of the substance shall take place in accordance with the Good Manufacturing Practice and in accordance with the dossier submitted.

Address: 7 Allée Kastner, CS 30026
F-67081 Strasbourg (France)
Tel: +33 (0) 3 88 41 30 30 – Fax: +33 (0) 3 88 41 27 71 - e-mail: cep@edqm.eu
Internet: http://www.edqm.eu

Failure to comply with these provisions will render this certificate void.

This certificate is granted within the framework of the procedure established by the European Pharmacopoeia Commission [Resolution AP-CSP (07) 1] for a period of five years starting from **12 October 2020**. Moreover, it is granted according to the provisions of Directive 2001/83/EC and Directive 2001/82/EC and any subsequent amendment, and the related guidelines.

This certificate has three annexes, the first of 1 page, the second of 3 pages and the third of 1 page.
This certificate has:
lines.

On behalf of the
Director of EDQM

Strasbourg, 12 October 2020

DECLARATION OF ACCESS *(to be filled in by the certificate holder under their own responsibility)*

SHREEGEN PHARMA LIMITED, as holder of the certificate of suitability

R0-CEP 2018-112-Rev 00 for Rosuvastatin calcium

hereby authorises .....
(*name of the pharmaceutical company*)

to use the above-mentioned certificate of suitability in support of their application(s) for the following Marketing Authorisation(s): (*name of product(s) and marketing number(s), if known*)

The holder also certifies that no significant changes to the operations as described in the CEP dossier have been made since the granting of this version of the certificate.

Date and Signature (*of the CEP holder*):

Address: 7 Allée Kastner, CS 30026
F-67081 Strasbourg (France)
Tel: +33 (0) 3 88 41 30 30 – Fax: +33 (0) 3 88 41 27 71 - e-mail: cep@edqm.eu
Internet: http://www.edqm.eu

Certification of Substances Department

Annex 1: Site(s) of production for R0-CEP 2018-112-Rev 00

Production of Rosuvastatin calcium:
SHREEGEN PHARMA LIMITED
PlotNo: 135F, KIDAB, Kolhar Industrial Area
Bidar District
India-585403 Karnataka

SHREEGEN PHARMA LTD

STANDARD TEST PROCEDURE	STP No. : RSA-005-01	Effective date: 13-01-2020
	Supersedes : RSA-005-00	Dated : 05-09-2015
	Department : Quality Control	Next review: December -2022

TITLE: ROSUVASTATIN CALCIUM **REFERENCE: Ph.Eur**

Residual solvents by GC:

Chromatographic conditions:

System	:	Gas Chromatograph with capillary column and Flame ionization detector
Column	:	DB – WAX or equivalent is suitable
Column dimensions	:	30 m X 0.53 mm ID, 1.00µm film thickness
Temperature	:	40°C for 8 minutes then rise at 15°C/min to 190°C hold for 2 minutes, then rise at 35°C/min to 220°C and hold for 10 minutes
Injector port temperature	:	140°C
Split ratio	:	1: 2
Detector port temperature	:	220°C
Air	:	300 ml/min
Hydrogen	:	30 ml/min
Make up gas (N_2 or He)	:	25 ml/min
Carrier gas (N_2 or He)	:	25 cm/sec (Linear velocity) constant flow mode

SHREEGEN PHARMA LTD		
STANDARD TEST PROCEDURE	STP No. : RSA-005-01	Effective date: 13-01-2020
	Supersedes : RSA-005-00	Dated : 05-09-2015
	Department : Quality Control	Next review: December -2022
TITLE: ROSUVASTATIN CALCIUM		REFERENCE: Ph.Eur

Injection volume : 1 µl

Diluent : 1-methyl-2pyrrolidone

Standard solution preparation:

- Weigh about 600 mg of Methanol, 120 mg of dichloromethane, 1000 mg of methyl tertiary butyl ether, 178 mg of toluene and 1000 mg of dimethyl sulfoxide into a 100 mL volumetric flask containing 10 mL diluent. Dissolve and dilute to the volume with diluent.
- Take 1 mL of the above solution into a 100 mL volumetric flask and dilute to the volume with diluent.

Test Solution preparation:

Weigh accurately about 200 mg of test sample into a 10 mL volumetric flask.

Dissolve and dilute to the volume with diluent.

Procedure:

- Equilibrate the column for 30 minutes at 220°C and then cool to 40°C.
- Inject 1µL diluent into the system and record the chromatogram as blank.
- Program the data processor to inhibit the integration of peaks due to diluent.
- Inject 1 µL of the standard solution for three times and record the peak areas of methanol, dichlorolmethane, methyl tertiary butyl ether, toluene and dimethyl sulfoxide.
- Inject 1µL of the test solution and record the peak areas of methanol, dichlorolmethane, methyl tertiary butyl ether, toluene and dimethyl sulfoxide.
- Inject 1µL of the standard solution for three times and record the peak areas of methanol,

SHREEGEN PHARMA LTD			
STANDARD TEST PROCEDURE	STP No. : RSA-005-01	Effective date: 13-01-2020	
	Supersedes : RSA-005-00	Dated : 05-09-2015	
	Department : Quality Control	Next review: December -2022	
TITLE: ROSUVASTATIN CALCIUM		REFERENCE: Ph.Eur	

dichlorolmethane, methyl tertiary butyl ether, toluene and dimethyl sulfoxide.

- The test is valid only if the RSD of six injections of standard solution is less than 15%.
- The resolution between the peaks due to methanol and dichloromethane should be not less than 2.0.
- Determine the amount of the residual solvents in the sample using the following formula:

Calculation:

$$\frac{\text{Sample area x Standard weight x 1 x 10 x 1000000}}{\text{Standard area x 100 x 100 x Sample weight}}$$

SHREEGEN PHARMA LTD, BIDAR

ROSUVASTATIN CALCIUM ELEMENTAL IMPURITIES

RISK MANAGEMENT SUMMARY

Intended route of administration: Oral				
Element	**Class**	**Intentionally added?**	**Considered in risk management?**	**Conclusion**
Cd	1	No	Yes	Absent
Pb	1	No	Yes	Absent
As	1	No	Yes	Absent
Hg	1	No	Yes	Absent
Co	2A	No	Yes	Absent
V	2A	No	Yes	Absent
Ni	2A	No	Yes	Absent
Tl	2B	No	No	--
Au	2B	No	No	--
Pd	2B	No	No	--
Ir	2B	No	No	--
Os	2B	No	No	--
Rh	2B	No	No	--
Ru	2B	No	No	--
Se	2B	No	No	--
Ag	2B	No	No	--
Pt	2B	No	No	--
Li	3	No	Yes	Absent
Sb	3	No	Yes	Absent
Ba	3	No	No	--
Mo	3	No	Yes	Absent
Cu	3	No	Yes	Absent
Sn	3	No	No	--
Cr	3	No	Yes	Absent

Absent: Results less than 30% of ICH Q3D option 1 limit.