Certification of Substances Department

KREATIVE ORGANICS PRIVATE LIMITED
Dr Krishnamohan SEELAMSETTY
Plot No.1306, Road No.65
Jubilee hills
India-500 033 Hyderabad, Telangana

CEP_RZ_PH_2016-056-1221557
MFE / spc

Strasbourg, 21 June 2019

Re: R0-CEP 2016-056-Rev 00 / Hydroxyzine hydrochloride

Dear Dr SEELAMSETTY,

Please find enclosed the certificate granted for **Hydroxyzine hydrochloride** following the evaluation of the dossier.

If you find a mistake on the CEP, you should notify EDQM within 3 months. After this deadline, any complaint will no longer be considered valid.

You are informed that the EDQM may share the assessment reports for this application with the National Competent Authorities of the Ph. Eur. Member states, and with the EMA including EMA committees and working parties/groups and the members and experts thereof.

In accordance with Resolution AP-CSP (07) 1, and as mentioned on the certificate, the submitted dossier must be updated after any change to its content, and this must be reported to EDQM.

This certificate is valid 5 years. It is your responsibility to ask for the renewal of the certificate in due time.

Yours faithfully,

Alma KISO
Scientific Officer

Hélène BRUGUERA
Head of Department

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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
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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 2016-056-Rev 00

Name of the substance:
HYDROXYZINE HYDROCHLORIDE

Name of holder:
KREATIVE ORGANICS PRIVATE LIMITED
Plot No.1306, Road No.65
Jubilee hills
India-500 033 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 **HYDROXYZINE HYDROCHLORIDE** no. 916 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.

Any unspecified impurity detected by the test for related substances of the monograph is limited to not more than 0.10%.

– Test for residual solvents by gas chromatography (Annex 2)
Isopropanol not more than 5000 ppm

No elemental impurity classified in ICH Q3D is intentionally introduced in the manufacture of the substance.

The re-test period of the substance is 60 months if stored under nitrogen in a double polyethylene bag (outer black) placed in a polyethylene drum.

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.

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

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 **21 June 2019**. 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 two annexes, the first of 1 page and the second of 3 pages.
This certificate has:
lines.

On behalf of the
Director of EDQM

Strasbourg, 21 June 2019

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

KREATIVE ORGANICS PRIVATE LIMITED, as holder of the certificate of suitability

R0-CEP 2016-056-Rev 00 for Hydroxyzine hydrochloride

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*):

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F-67081 Strasbourg (France)
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Certification of Substances Department

Annex 1: Site(s) of production for R0-CEP 2016-056-Rev 00

Production of Hydroxyzine hydrochloride:
KREATIVE ORGANICS PRIVATE LIMITED
D-123, Phase-III, I.D.A. Jeedimetla
India-500 055 Hyderabad, Telangana

Kreative Organics

HYDROXYZINE HYDROCHLORIDE EP TEST PROCEDURES

B. Test Procedures		
Sl. No.	**Test Parameters**	**Test Procedure**
12.	Residual Solvents (GC)	***Standards and Reagents***: Solvents of Dimethylformamide, Isopropanol (IPA) and Toluene are used for the standard preparation and N2 gas (GC grade) is used as a carrier gas. ***Column***: (a) Size – 30M x 0.53mm ID and 3µm film thickness (USP – G 43). (b) Stationary phase – end capped 6% cynopropylphenyl-94% Dimethylpolysiloxane. ***Diluent:*** Dimethylformamide (DMF). ***Blank:*** DMF

HYDROXYZINE HYDROCHLORIDE EP TEST PROCEDURES

B. Test Procedures

Sl. No.	Test Parameters	Test Procedure
		Standard Solution: 10ppm solution of Isopropanol(IPA) and Toluene : Transfer 32µL of IPA and 29µL of toluene into a 25mL volumetric flask and dilute with DMF to volume and mix. Take 1mL of this solution into a 100mL volumetric flask and dilute with DMF to volume and mix. ***Test Solution***: Weigh accurately 750mg of test sample dissolve with 5mL of DMF. ***Chromatographic Conditions:*** Flow rate - 4.00mL / minute Detector - FID Injector port temperature - 140^{0}C Detector port temperature - 260^{0}C Column oven temperature - 45^{0}C (hold for 5 minutes) then raise to 120^{0}C @ 25^{0}C per minute (hold for 2 minutes) then raise to 230^{0}C @ 35^{0}C per minute (hold for 2 minutes). Equilibrium time - 1 minute. Split - 10 ***Head Space Parameters:*** G.C Cycle Time - 28.00 min Valve Oven Temp - 100^{0}C Transfer Line Temp - 110^{0}C Standby Flow Rate - 100 ml/min Platen/Sample Temp - 80^{0}C Platen Temp Equil. Time - 1.00 min Sample Equil. Time - 10.00 min Pressurize - 10 PSIG Pressurize Time - 2.00 min

HYDROXYZINE HYDROCHLORIDE EP TEST PROCEDURES

B. Test Procedures

Sl. No.	Test Parameters	Test Procedure

Pressurize Equil. Time - 0.20 min
Loop Fill Pressure - 5 PSIG
Loop Fill Time - 2.00 min
Inject Time - 1.00 min

Procedure:

1. Condition the column for at least 30 minutes and ensure no peaks are eluting from the column. Allow to equilibrate the column.
2. Take 5mL of standard solution and transfer in to a vial for each injection.
3. Take 5mL of test solution and transfer in to a vial for each injection.
4. ***Order of sequence***:

Sl. No.	Order of sequence	No.of Injections
1.	Blank	02
2.	System Suitability (Standard solution)	06
3.	Blank	01
4.	Test Sample	02

5. ***System Suitability:*** Inject system suitability solution for system suitability and check the Resolution & RSD% peak areas of IPA and Toluene.

Acceptance criteria:

1. Resolution between IPA and Toluene : NLT 2.0
2. RSD for peak area of IPA and Toluene : NMT 15.0%

Calculation:

Determine the amount in ppm using following formula:

$$ppm = \frac{\text{Sample Area}}{\text{Standard Area}} \times \frac{\text{Standard concentration } \mu g/mL}{\text{Sample concentration } \mu g/mL} \times 10^6$$