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

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

CEP_RZ_PH_2019-247-1331645
ORE / mr

Strasbourg, 30 November 2020

Re: R0-CEP 2019-247-Rev 00 / Bisacodyl

Dear Dr SEELAMSETTY,

Please find enclosed the certificate granted for **Bisacodyl** 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,

Hélène BRUGUERA
Head of Department

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
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edqm
European Directorate for the Quality of Medicines & HealthCare | Direction européenne de la qualité du médicament & soins de santé
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Certification of Substances Department

Certificate of suitability
No. R0-CEP 2019-247-Rev 00

Name of the substance:
BISACODYL

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 **BISACODYL** no. 595 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

In the last steps of the synthesis acetone is used as solvent. Its residual content is limited by the test for loss on drying described in the monograph, with a limit of not more than 0.5%.

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

The re-test period of the substance is 60 months if stored double polyethylene bags, 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.

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F-67081 Strasbourg (France)
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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 **30 November 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 5 pages, and the third of 1 page.
This certificate has:
lines.

On behalf of the
Director of EDQM

Strasbourg, 30 November 2020

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 2019-247-Rev 00 for Bisacodyl

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)
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Internet: http://www.edqm.eu

Certification of Substances Department

Annex 1: Site(s) of production for R0-CEP 2019-247-Rev 00

Production of Bisacodyl:
KREATIVE ORGANICS PRIVATE LIMITED
D-123, Phase-III, I.D.A. Jeedimetla Village
Quthbullapur Mandal, Medchal-Malkajgiri District
India-500 055 Hyderabad, Telangana

RESIDUAL SOLVENTS BY GC:

Apparatus :

Head space GC

Volumetric flasks

Pipette

Sonicator

Reagents:

Dimethyl sulphoxide

Acetone

Methanol

Method

Chromatographic Conditions:

Detector : Flame ionization detector

Column : a) Size – 30M x 0.53mm ID and 3µm film thickness(ZB – 624)

b) Stationary phase – end capped 6% cynopropylphenyl-94% dimethyl polysiloxane.

Column oven temperature: 45^0C (hold for 4 minutes) then raise to 120^0C @ 25^0C per minute (hold for 2 minutes) then raise to 230^0C @ 35^0C per minute (hold for 2 minutes)

Injector port temperature	-	150^0C
Detector port temperature	-	260^0C
Equilibrium time	-	1 minute.
Split ratio	-	10:1
Flow rate	-	4.0 mL/min
Carrier gas	-	N2
Hydrogen flow	-	40mL/min
Air flow	-	400mL/min
Make up flow	-	30mL/min
Diluent	-	DMSO
Run time	-	20min

Agilent technologies 7697A Head space auto sampler :

G.C Cycle Time	-	40.00 min
Vial Oven Temp	-	80^0C
Loop Temp	-	100^0C
Transfer line Temp	-	110^0C
Standby Flow Rate	-	100 mL/min
Platen Temp Equil. Time	-	1.00 min
Vial Equil. Time	-	15.00 min
Pressurize Time	-	2.00 min
Pressurize Equil. Time	-	0.30 min
Inject Time	-	1.00
Vial agitation	-	High

Standard stock solution preparation: Transfer 0.12g of Methanol and 0.2g of Acetone transfer into a 100ml volumetric flask containing about 40 mL of diluent and make up to the mark with diluent.

Standard solution Preparation: Dilute 10 mL of standard stock the solution containing about 100 mL volumetric flask containing about 40 mL diluent and make up to the mark with the same diluent mix well.

Blank preparation: Pipette out 5 mL of diluent into a 20 mL head space vial and crimp it immediately and insert into sample tray.

Standard solution Preparation: Pipette out 5 mL of standard solution into a 20 mL head space vial and crimp it immediately.

Sample Solution Preparation: Transfer about 0.20g of test sample in a 20 mL head space vial and crimp it immediately. (Duplicate preparation)

Procedure:

Condition the column for at least 30 minutes and ensure no peaks are eluting from the Column. Allow to equilibrate the column.

Order of sequence:

Sl. No.	Order of sequence	No. of Injections
1.	Blank	01
2.	Standard solution	06
3.	Blank	01
4.	Test Sample-1	01
5.	Test Sample-2	01
6.	Standard solution/BKT	01

System Suitability: Inject standard solution for system suitability and check the Resolution & RSD% peak areas of Methanol and Acetone.

Acceptance criteria:

Resolution between Methanol & Acetone is : NLT 1.5

RSD for peak area of Methanol & Acetone is : NMT 15.0%

If identified any peaks in the blank, that area can be subtracted from the standard Solutions or Test solutions.

Take the mean area's for calculations.

Calculation:

Content of Solvent:

$$\frac{(A-B) \times W1 \times 10 \times 5}{(C-B) \times 100 \times 100 \times W2} \times \frac{P}{100} \times 10^{6}$$

Where

A = Peak area response of respective solvent obtained in the sample chromatogram

B =is average area response of respective solvent interference from Blank

C =is average area response of respective solvent obtained in the standard chromatogram

W1= is respective solvent weight in standard solution

W2= is weight of sample in grams

Elemental Impurities Risk assessment Summary:

Intended route of administration/Use of the Substance: Bisacodyl Oral dosage form				
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	No risk identified
Au	2B	No	No	No risk identified
Pd	2B	No	No	No risk identified
Ir	2B	No	No	No risk identified
Os	2B	No	No	No risk identified
Rh	2B	No	No	No risk identified
Ru	2B	No	No	No risk identified
Se	2B	No	Yes	Absent
Ag	2B	No	No	No risk identified
Pt	2B	No	No	No risk identified
Li	3	No	No	No risk identified
Sb	3	No	No	No risk identified
Ba	3	No	No	No risk identified
Mo	3	No	No	No risk identified
Cu	3	No	No	No risk identified
Sn	3	No	No	No risk identified
Cr	3	No	No	No risk identified

Note: "Absent" (meaning less than 30% of ICH Q3D option 1 limit, as defined under 3.1.1 of "Implementation of ICH Q3D in the Certification Procedure" PA/PH/CEP (16) 23, 1R guidance.