

Certification of Substances Division

Rusan Pharma Ltd.

Regulatory Affairs Department
58-D, Government Industrial Estate
Charkop, Kandivli (West)
India-400 067 Mumbai

CEP_RZ_PH_2007-065-0331511

Strasbourg, 16 November 2009

FK / bho

Re: R0-CEP 2007-065-Rev 00 / Buprenorphine

Dear Sirs,

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

In accordance with Resolution AP-CSP (07) 1, and as mentioned on the certificate, the submitted dossier must be updated after any significant change that may alter the quality, safety or efficacy of the substance. This must be reported to us so that the certificate can be updated (if relevant after reassessment).

This certificate is valid 5 years. It is your responsibility to ask for the renewal of the certificate and to update your dossier in due time (e.g. about 6 months prior to expiry date).

Yours faithfully,



Pascale POUKENS-RENWART
Scientific Officer
Certification of Substances Division



Hélène BRUGUERA
Deputy Head
Certification of Substances Division

Cc.: Mrs Jo BUNYAN-CALLISTO CONSULTING

Certification of Substances Division

**Certificate of suitability
No. R0-CEP 2007-065-Rev 00**

1 *Name of the substance:*

2 **BUPRENORPHINE**

3 *Name of holder:*

4 **RUSAN PHARMA LTD.**

5 58-D, Government Industrial Estate

6 Charkop, Kandivli (West)

7 India-400 067 Mumbai

8 *Site(s) of production:*

9 **RUSAN PHARMA LTD.**

10 Plot No 6406, G.I.D.C.

11 Near Hoechst Chokadi, Dist. Bharuch

12 India-393 002 Ankleshwar, Gujarat

13 After examination of the information provided on the manufacturing method and
14 subsequent processes (including purification) for this substance on the site(s) of
15 production mentioned above, we certify that the quality of the substance is suitably
16 controlled by the current version of the monograph **BUPRENORPHINE** no. 1180 of the
17 European Pharmacopoeia, current edition including supplements, only if it is
18 supplemented by the test(s) mentioned below, based on the analytical procedure(s)
19 given in annex.

20 — Test for residual solvents by gas chromatography (Annex 1)

21 Ethylacetate not more than 1000 ppm

22 Chloroform not more than 60 ppm

23 Acetonitrile not more than 410 ppm

24 The re-test period of the substance is 5 years if stored in double laminated aluminium
25 sachet.

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

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

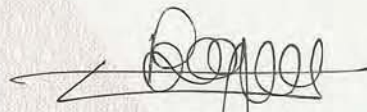
30 Manufacture of the substance shall take place in accordance with the Good
31 Manufacturing Practice and in accordance with the dossier submitted.

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

33 This certificate is granted within the framework of the procedure established by the
34 European Pharmacopoeia Commission [Resolution AP-CSP (93) 5 as amended] for a
35 period of five years starting from **16 November 2009**. Moreover, it is granted according
36 to the provisions of Directive 2001/83/EC and Directive 2001/82/EC and any
37 subsequent amendment, and the related guidelines.

38 This certificate has one annex of 2 pages.

39 This certificate has:
40 lines.


On behalf of the
Director of EDQM



Strasbourg, 16 November 2009

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

Rusan Pharma Ltd., as holder of the certificate of suitability

R0-CEP 2007-065-Rev 00 for BUPRENORPHINE

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)*:

RUSAN PHARMA LTD.
ANALYTICAL METHOD VALIDATION

For Restricted Circulation only

PROTOCOL No.: AMV/B-1001B/Res.Sol./02			Issued By: Q.A.
Product: Residual Solvents – Methanol, Ether, Acetone, Acetonitrile, Ethyl acetate, Chloroform, Cyclohexane & Toluene in Buprenorphine			
DOC No.	Issue Date	Effective Date	Supercedes No.
1.0			NIL

7.0 ANALYTICAL METHOD TO BE USED: In-house

RESIDUAL SOLVENTS – Methanol, Ether, Acetone, Acetonitrile, Ethyl acetate, Chloroform, Cyclohexane & Toluene in Buprenorphine (By Gas Chromatography)

PARAMETERS: -

Column : DB-624 , Capillary column
30 m x 0.32 mm,
Film thickness 1.8 micron
(6% Cyanopropylphenyl– 94% dimethylpolysiloxane)

Column Temperature : 40⁰C for 5.0 minutes
200⁰C at 20 deg C / minute
200⁰C for 10 minutes

Injector Temperature : 140⁰C

Detector Temperature (FID) : 250⁰C

Flow of carrier gas : 0.98 ml / min of Nitrogen

Chloroform stock solution:

Transfer about 180 mg Chloroform, accurately weighed to a 100 ml volumetric flask, containing 80 ml of Dimethylformamide, shake. Dilute to 100 ml with Dimethylformamide.

Standard stock solution:

Transfer about 150 mg accurately weighed of each of the following, Methanol, Ether, Acetone, Ethyl acetate & Cyclohexane, about 75 mg of each of Toluene, Acetonitrile & 10 ml of Chloroform stock solution, to a 100 ml volumetric flask containing 80 ml Dimethylformamide, Shake & dilute to 100 ml with Dimethylformamide (I).

Dilute 1 ml of (I) to 10 ml with Dimethylformamide (II)

Place 1 ml of std solution (II) in a vial.

RUSAN PHARMA LTD.
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Product: Residual Solvents – Methanol, Ether, Acetone, Acetonitrile, Ethyl acetate, Chloroform, Cyclohexane & Toluene in Buprenorphine			
DOC No.	Issue Date	Effective Date	Supercedes No.
1.0			NIL

Sample Preparation:

Take about 1500mg of sample in a 5 ml volumetric flask add 5ml of Dimethylformamide, shake to dissolve.

Place 1 ml of sample preparation in a vial.

Procedure: Heat thermostatically in Head space, Inject standard & sample in triplicate and record the peak responses.

Calculation:

For solvents other than Chloroform (Methanol, Ether, Acetone, Ethyl acetate & Cyclohexane, Toluene, and Acetonitrile):

$$\frac{\text{Sample area} \times \text{Wt. of std in mg} \times 1 \times 1 \times 5 \times 1 \times 1000000}{\text{Standard area} \times 100 \times 10 \times \text{wt. of sample in mg}}$$

= Content in ppm

For Chloroform:

$$\frac{\text{Sample area} \times \text{Wt. of std in mg} \times 10 \times 1 \times 1 \times 5 \times 1 \times 1000000}{\text{Standard area} \times 100 \times 100 \times 10 \times \text{Wt. of sample in mg}}$$

= Content in ppm