Re: R0-CEP 2001-311-Rev 00 / LISINOPRIL DIHYDRATE

Dear Mr Patil,

Please find enclosed the certificate granted for LISINOPRIL DIHYDRATE following the evaluation of the dossier.

In answer to Industry's request concerning the control of the use of copies of certificates of suitability by customers in marketing applications, a declaration of access box has been introduced at the bottom of the certificate of suitability with the same purpose as the letter of access for an EDM. It is your responsibility to fill in this declaration at your convenience.

Please note that a copy of this certificate has to be forwarded to your customers and any concerned competent authority to allow them to update their documentation and in particular the concerned marketing authorisations.

In accordance with Resolution AP-CSP (99) 4, and as mentioned on the certificate, the submitted dossier must be updated every five years or after any significant modification of the manufacturing method that may alter the quality, safety or efficacy of the product or require changing the specifications of the monograph. This must be reported to us so that the certificate can be updated (if relevant after reassessment).

Failure 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) may lead to a gap between the expiry date of the original certificate and the granting of the renewed certificate. In the absence of a request for renewal of the certificate, it will definitively expire at the end of its 5-year validity, and this will be mentioned in the lists of granted certificates published in Phareuropa and on the EDQM website. A new application would then have to be filed to obtain a new certificate for the same substance. Please note that no reminder will be sent by EDQM.

This certificate does not replace a batch analysis certificate.

Yours faithfully,

Susanne BARREK
Scientific Officer

Corinne POUGET
Head of Certification Unit

226 Avenue de Colmar
(entrance rue Schertz)
B.P. 907
F-67029 Strasbourg Cedex

Tél.: +33 (0)3 88 41 30 30
Fax: +33 (0)3 88 41 27 71

E-mail: certification@phear.org
http:// www.phear.org
Certificate No. RO-CEP 2001-311-Rev 00

1 Name of the substance:
2 Lisinopril Dihydrate

3 Name of holder:
4 Lupin Limited
5 159 C S T Road, Kalina
6 Santacruz (East)
7 IND - 400 098 Bombay

8 Site of production:
9 Lupin Limited
10 198-201 New Industrial Area No 2
11 Mandideep
12 IND - 462 046 Dist Raisen, Madhya Pradesh

13 After examination of the information provided on the manufacturing method and subsequent processes (including purification) for this substance on the site of production mentioned above, IND - 462 046 Dist Raisen, Madhya Pradesh, we certify that the quality of the substance is suitably controlled by the monograph Lisinopril Dihydrate (no. 1120, Ph. Eur. 4th Ed. and any subsequently revised version) only if it is supplemented by the test(s) mentioned below, based on the analytical procedure(s) given in annex.

19 — Test for residual solvents by gas chromatography (Annex 1)
20 Ethanol not more than 1000 ppm

21 The submitted dossier must be updated every five years or after any significant modification of the manufacturing method that may alter the quality, safety or efficacy of the product or require changing the specifications of the monograph.

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

26 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 (93) 5 as amended] for a period of five years starting from 23 June 2004. 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 32 lines and one annex of 2 pages.

Dr. A. ARTIGES
Director of the Quality of Medicines

Strasbourg, 23 June 2004

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

LUPIN LIMITED, as holder of the certificate of suitability

R0-CEP 2001-311-Rev 00 for LISINOPRIL DIHYDRATE

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)

Date and Signature (of the CEP holder):

Postal Address: 226 Avenue de Colmar (entrance rue Schertz) B.P. 907 — F 67029 Strasbourg Cedex 1
Telephone: 03.88.41.30 30 - Fax 03.88.41.27.71 - E-mail: certification@pheur.org
Organic Volatile Impurity / Residual Solvents:

Chemicals and Reagents:
1. Ethyl Alcohol W.S.
2. Methylene chloride W.S.
3. Toluene W.S.

Gas Chromatographic Parameters:
1) Column: DB-1 column 30 m x 0.53 mm
2) Oven temperature: 30°C
3) Injection Temperature: 150°C
4) Detector Temperature: 250°C
5) Carrier Gas: Nitrogen
6) Carrier gas pressure: 9.5 psig

Head Space Parameters:
Aux. Temperature: 80°C
Heating Time: 35 min.
Injection Time: 0.1 min.

System Suitability Parameters:
Resolution between two consecutive peaks: NLT 3
RSD (6 Injections): NMT 15%
Tailing Factor: NMT 2.5%

Preparation and Head Space Sampler vials:
Heat Head Space sample vials and septa in an oven at 100°C for atleast 8 hours before use. Keep all the vials, that will be used for the experiment, away from the areas of high solvent usage.

Standard Preparation:
Solution – A:
In a 100 ml volumetric flask take about 10 ml of water, weigh accurately about 0.2 gm of Ethyl Alcohol and make up the volume to 100 ml with water.

Solution – B:
In a 100 ml volumetric flask take about 10 ml of Dimethyl Sulphoxide, weigh accurately about 0.1 gm of Methylene Chloride, 0.1 gm of Toluene and make up the volume to 100 ml with Dimethyl Sulphoxide. Dilute 10 ml of this solution to 50 ml with Dimethyl Sulphoxide.

Further dilute 5 ml of solution-A and 5 ml of solution-B to 200 ml with water. This solution contains Ethyl alcohol 50 ppm, Methylene chloride 5 ppm & Toluene 5 ppm.
Section : 1.5.2  TITLE : TEST METHODS

Blank Solution:
Dilute 5 ml of Dimethyl Sulphoxide to 200 ml with water.

Standard Solution Vial:
Transfer 1.0 ml of standard preparation into a Headspace sample vial.

Test Vial:
Weigh accurately about 50 mg of test sample into a head space sample vial, add 1.0 ml blank solution into the vial.

Heat the standard and sample vials for 35 min. at 80°C. Inject the standard sample solution into Gas Chromatograph.

Calculation:
\[
\text{Content (ppm)} = \frac{A_t}{A_s} \times \frac{C}{W} \times 10^6
\]

At = Area response of each solvent in the test sample
As = Area response of corresponding solvent in the standard preparation
C = Weight of individual solvent in mg/ml
W = Weight of test in mg.
10^6 = To obtain results in ppm