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. R1-CEP 2003-096-Rev 01

Name of the substance:
NYSTATIN

Name of holder:
ANTIBIOTICE SA
1 Valea Lupului Street
Romania-707410 Iasi

Site(s) of production:
SEE ANNEX 1

THIS CERTIFICATE SUPERSEDES THE PREVIOUS CERTIFICATE
R1-CEP 2003-096-REV 00

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 **NYSTATIN** no. 517 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)

Acetone	not more than 0.5%
Methanol	not more than 0.3%

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 36 months if stored protected from light at a temperature between 2°C and 8°C in a double polyethylene bag placed inside a cardboard box.

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.

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

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 renewed from **13 May 2010** according to the provisions of Resolution AP-CSP (07) 1, and 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 2 pages and the third of 1 page.

This certificate has:

lines.

On behalf of the
Director of EDQM

Strasbourg, 25 September 2018

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

Antibiotice SA, as holder of the certificate of suitability

R1-CEP 2003-096-Rev 01 for Nystatin

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 R1-CEP 2003-096-Rev 01

Production of Nystatin:
Antibiotice SA
1 Valea Lupului Street
Romania-707410 Iasi

Content of acetone and methanol

Apparatus:
- Gas chromatograph
- Headspace autosampler
- Analytical balance

Reagents:
- Methanol R
- Acetone R
- N,N-dimethylformamide R

Preparation of solutions:

Test solution:
Dissolve a quantity of about 0.250 g of nystatin substance to be examined in *N,N-dimethylformamide R* in a 25 ml volumetric flask. Dilute to volume with the same solvent. Place 5 ml of the resulting solution in a vial for injection and add 1 ml of *N,N-dimethylformamide R.*

Reference solution:
Dilute 0.300 g of methanol R and 0.500 g of acetone R with *N,N-dimethylformamide R* in a 100 ml volumetric flask. Dilute 1 ml of the solution with the same solvent to 100 ml. Place 5 ml of the resulting solution in a vial for injection and add 1 ml of *N,N-dimethylformamide R.*

Blank solution: Place 6 ml of *N,N-dimethylformamideR* in a vial for injection.

Close the vials with a tight rubber membrane stopper coated with polytetrafluoroethylene and secure with an aluminium crimped cap. Shake to obtain a homogeneous solution.

Working parameters of the static headspace:
- Equilibration temperature: 105°C
- Equilibration time: 45 minutes
- Transfer line temperature: 110°C
- Carrier gas: nitrogen for chromatography or helium for chromatography
- Pressurisation time: 30 seconds
- Injected volume: 1 ml

Chromatographic system:
- Chromatographic column: fused-silica capillary or wide-bore column 30 m long and 0.32 mm or 0.53 mm in internal diameter coated with *macrogol 20 000 R* (film thickness: 0.25 µm),

- Carrier gas: nitrogen for chromatography or helium for chromatography,
- Split ratio: 1:5,
- Linear velocity: 35 cm/s,
- Detector: Flame ionisation detector,
- Column temperature: maintain the temperature of the column at 50°C for 20 min, then raise the temperature at a rate of 6°C/min to 165°C and maintain it at 165°C for 20 min,
- Injector temperature: 140°C,
- Detector temperature: 250°C.

Procedure:
Set the working conditions for the headspace device and the gas chromatograph and allow them to stabilize. Place the vials containing the test solution, reference solution and the blank solution in the headspace device and start operate. Record the chromatograms corresponding to each solution and measure the areas of the solvents' peaks. Disregard the peak due to the blank solution.

Calculate the contents of residual solvents by the formula:

$$\% = \frac{A_T \cdot m_{RS}}{A_{RS} \cdot m_T \cdot 4}$$

Where:
A_T = area of the solvent peak in the chromatogram obtained with the test solution,
A_{RS} = area of the solvent peak in the chromatogram obtained with the reference solution,
m_{RS} = mass of the solvent used to prepare the reference solution, in grams,
m_T = mass of substance to be examined used to prepare the test solution, in grams.

Table no. 4 - Nystatin –Risk management summary for elemental impurities

Intended route of administration / Use of the substance : 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	No	Absent
V	2A	No	No	Absent
Ni	2A	No	Yes	Absent
Tl	2B	No	No	Absent
Au	2B	No	No	Absent
Pd	2B	No	No	Absent
Ir	2B	No	No	Absent
Os	2B	No	No	Absent
Rh	2B	No	No	Absent
Ru	2B	No	No	Absent
Se	2B	No	No	Absent
Ag	2B	No	No	Absent
Pt	2B	No	No	Absent
Li	3	No	No	Absent
Sb	3	No	No	Absent
Ba	3	No	Yes	Absent
Mo	3	No	Yes	Absent
Cu	3	No	Yes	Absent
Sn	3	No	No	Absent
Cr	3	No	Yes	Absent

Note : *Absent* means that test results are less than 30% of ICH Q3D, Option 1.