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 2003-105-Rev 01

Name of the substance:
CICLOSPORIN

Name of holder:
HANGZHOU ZHONGMEI HUADONG PHARMACEUTICAL CO., LTD.
866 Moganshan Road
China-310 011 Hangzhou, Zhejiang Province

Site(s) of production:
SEE ANNEX 1

THIS CERTIFICATE SUPERSEDES THE PREVIOUS CERTIFICATE
R1-CEP 2003-105-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 **CICLOSPORIN** no. 994 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 0.1%.

– Test for residual solvents by gas chromatography (Annex 2)

Acetone	not more than 1000 ppm
Petroleum ether	not more than 100 ppm

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

The re-test period of the substance is 3 years if stored in a polyethylene bag in an aluminium foil plastic compound film bag, placed in an aluminium container.

The holder of the certificate has declared the use of material of human or animal origin in the manufacture of the substance and there is no risk of viral contamination.

After examination of the information provided on the origin of raw material(s) and type of tissue(s) used and on the manufacturing process for this substance on the site(s) of production listed in annex, we certify that the substance **CICLOSPORIN** meets the criteria described in the current version of the monograph Products with risk of transmitting agents of animal spongiform encephalopathies no. 1483 of the European Pharmacopoeia, current edition including supplements.

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

The submitted dossier must be updated after any significant change that may alter the quality, safety or efficacy of the substance, or that may alter the risk of transmitting animal spongiform encephalopathy agents.

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.

The certificate is valid provided that there has been no deterioration in the TSE status of the country(ies) of origin of the source material.

This certificate is renewed from **10 November 2011** 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 3 pages and the third of 2 pages.
This certificate has:
lines.

On behalf of the
Director of EDQM

Strasbourg, 2 September 2021

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

Hangzhou Zhongmei Huadong Pharmaceutical Co., Ltd., as holder of the certificate of suitability

R1-CEP 2003-105-Rev 01 for Ciclosporin

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 2003-105-Rev 01

Production of Ciclosporin :

Hangzhou Zhongmei Huadong Pharmaceutical Co., Ltd.
866 Moganshan Road
China-310 011 Hangzhou, Zhejiang Province

JOYANG LABORATORIES
N°9 Haidu North Road
Sheyang Economic Development Zone
China-224 300 Yancheng, Jiangsu Province

Residual Solvents

— Instruments and apparatus: Gas chromatography (capillary column - Stabilwax Ø 0.25 mm×60 m×1.4 μm =DB-624, detector-FID); head-space bottle; auto-injector; volumetric pipette; graduated pipette

— Gas chromatographic conditions:

Carrier gas:	Nitrogen gas 1.5 ml/min
FID gas:	hydrogen gas at about 40 ml/min
	air at about 450ml/min
Sample injection temperature:	250°C
Column temperature:	keep at 40°C for 20 mins, then raise to 200°C by 40°C/min and keep for 8 mins

Detector temperature: 250°C

Head-space injector: 80°C, 30 min

Injection volume: 1 ml

— Reagents: Acetone(AR grade， 500 ml/396 g); petroleum ether (AR grade)

— Preparation:

Preparation of acetone reference solution and petroleum ether reference solution: Add sufficient dimethyl sulfoxide to a 100-ml volumetric flask. By difference, weigh on an analytical balance 0.1g (about 5-6 drops) of acetone and 0.01g of petroleum ether from a dropper, then add quickly to the volumetric flask. Stopper the flask, shake well and add more dimethyl sulfoxide to make up to volume.

Preparation of bottles of acetone reference and petroleum ether reference (at least prepare 8 bottles, and adjust the number according to the need): Accurately transfer 4 ml of dimethyl sulfoxide and 1 ml of acetone reference solution and petroleum ether reference solution into the head-space bottle, then seal the bottle.

Preparation of bottles of sample solution: (prepare 2 solutions for each batch) With a weighing paper, by difference, weigh accurately 1.00 g of Ciclosporin A on an analytical balance, into a 20-ml head-space bottle. Accurately add 5 ml of dimethyl sulfoxide and seal the bottle.

Preparation of Acetone location bottle: To a 100-mL volumetric flask add appropriate amount of dimethyl sulfoxide, add about 0.1g of acetone with analytical balance by dropping bottle, seal and mix well, dilute to the volume with dimethyl sulfoxide. To a 20-mL headspace vial transfer 4mL of dimethyl sulfoxide, add 1mL of solution above, and seal.

Preparation of Petroleum ether location bottle: To a 100-mL volumetric flask add appropriate amount of dimethyl sulfoxide, add about 0.01g of petroleum ether with analytical balance by dropping bottle, seal and mix well, dilute to the volume with dimethyl sulfoxide. To a 20-mL headspace vial transfer 4mL of dimethyl sulfoxide, add 1mL of solution above, and seal.

Preparation of blank: Transfer accurately 5 ml of dimethyl sulfoxide into a 20-ml head-space bottle and seal.

Preparation for the instrument: Put the head-space bottles into the head-space auto-injector in order, start the instrument according to SOP, and when the system is stable, carry out the procedure.

— Procedure for the testing of residual acetone:

a). System suitability tests:

Blank test: Inject the blank into the HPLC, record the chromatogram and it should be normal.

Repeated injection variant coefficient: Test at least 6 bottles of acetone reference solution and inject each once. Record the chromatogram and RSD of the peak areas obtained from the last six injections should be not more than 15%.

b). Examination:

Test two bottles of sample solutions from the first batch, and inject once for each and record the chromatograms. Calculate the residual acetone and get the average as the result.

Use the same method to test the sample from the second, third, fourth, and fifth batches. It cannot exceed five batches tested at one time.

Test the rest 2 bottles of acetone reference solution and petroleum ether reference solution. Inject each for once and record the chromatograms. The relative deviation of the peak areas should not be more than 30%, and get the average.

If more than five batches are tested at the same time, repeat the above procedure.

— Calculation the residual acetone:

— $$\text{Residual solvents (ppm)} = \frac{Ai}{As} \times \frac{Ws}{Wi} \times 10000$$

Where:

As is the acetone/petroleum ether peak area of the reference solution;

Ai is the acetone/petroleum ether peak area of the sample solution;

Ws is the weight of the acetone/petroleum ether reference, g;

Wi is the weight of CsA sample, g.

Elemental impurities in Ciclosporin based on the risk assessment

Intended route of administration / Use of the substance: Oral administration / Ciclosporin				
Elements	**Class**	**Intentionally added?**	**Considered in risk management**	**Conclusion**
Cd	1	No	Yes	Absence
Pb	1	No	Yes	Absence
As	1	No	Yes	Absence
Hg	1	No	Yes	Absence
Co	2A	No	Yes	Absence
V	2A	No	Yes	Absence
Ni	2A	No	Yes	Absence
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	No	No risk identified
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	Yes	Absence
Cu	3	No	Yes	Absence
Sn	3	No	No	No risk identified
Cr	3	No	Yes	Absence
Mn	/	No	Yes	Absence
Ti	/	No	Yes	Absence

"Absence" means less than 30% of ICH Q3D option 1 limit.