EUROPEAN DIRECTORATE FOR THE QUALITY OF MEDICINES & HEALTHCARE

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

COUNCIL OF EUROPE
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Certification of Substances Department

JPN PHARMA PVT LTD
Mr Mukund SHAH
T-108/109, M.I.D.C. Tarapur
District Palghar
India – 401 506 Boisar, Maharashtra

CEP 2021-092-P01
Procedure owner: NF

Strasbourg, 10 May 2023

Re: CEP 2021-092 / Trimetazidine dihydrochloride

Dear Mr Mukund SHAH,

Please find enclosed the certificate granted following the treatment of your dossier.

If you find a mistake on the CEP, you should notify the EDQM within 3 months. After this period, any complaint may no longer be accepted.

You are reminded that 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.

For any question regarding the application, please contact us using the following e-mail address: CEP@edqm.eu

Yours faithfully,

Certification of Substances Department

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 2021-092 - Rev 00

Name of the substance:
TRIMETAZIDINE DIHYDROCHLORIDE

Name of holder:
JPN PHARMA PVT LTD
T-108/109, M.I.D.C. Tarapur
District Palghar
India-401 506 Boisar, Maharashtra

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 **TRIMETAZIDINE DIHYDROCHLORIDE** no. 1741 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 0.10%.

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

Acetone	not more than 5000 ppm
Methanol	not more than 3000 ppm
2-Propanol	not more than 5000 ppm

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

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

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 – e-mail: cep@edqm.eu
Internet: https://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 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 **10 May 2023**. 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 3 pages and the third of 2 pages.
This certificate has:
lines.

On behalf of the
Director of EDQM

Strasbourg, 10 May 2023

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

JPN PHARMA PVT LTD, as holder of the certificate of suitability

R0-CEP 2021-092 - Rev 00 for Trimetazidine dihydrochloride

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*):

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

Annex 1: Site(s) of production for R0-CEP 2021-092 - Rev 00

Production of intermediate(s):

SHRI VINAYAK CHEMEX (INDIA) PRIVATE LIMITED
Plot No. T-11 M.I.D.C. Tarapur
District Palghar
India-401 506 Boisar, Maharashtra

Production of Trimetazidine dihydrochloride:

JPN PHARMA PVT LTD
T-108/109, M.I.D.C. Tarapur
District Palghar
India-401 506 Boisar, Maharashtra

Residual Solvent (By GCHS):

Procedure:

Chromatographic parameters:

Equipment	:	Gas chromatograph GC-2010 PLUS & Headspace Versa or equivalent
Column	:	DB-624, 30 m x 0.53 mm x 3.0 µm or equivalent.
Carries gas	:	Nitrogen
Carrier gas Pressure / Flow rate	:	3.4 psi
Detector	:	FID
Injector temperature	:	140°C
Injection mode	:	Split
Split ratio	:	1: 5
Detector temperature	:	240°C
Signal acquire	:	40 msec
H2 flow	:	40 ml / min.
O2 flow	:	400 ml / min.
Oven temperature	:	Initial temperature 40°C for 2 min. Ramp rate 5°C/min. final temperature 200°C for 1 min.
Equilibration time	:	3.0 min.

Total Program Time	:	35.00min
Headspace Conditions		
GC cycle time	:	40.0 min
Valve oven temperature	:	105°C
Transfer line temperature	:	110°C
Platen / sample temperature	:	100°C
Platen temperature equil. time	:	1.0 min
Sample equil. time	:	20 min
Mixer	:	On
Mixing level	:	Medium
Mixing time	:	1 min
Mixer stabilize time	:	0.5 min
Pressurize	:	12 psig
Pressurize time	:	1 min
Pressurize equil. Time	:	0.2 min
Loop fill pressure	:	5 psig.
Loop fill time	:	0.20min.
Inject time	:	0.22min

Preparation of Diluent:

Pipette out 50ml of Dimethylsulfoxide in 500ml volumetric flask, Dissolve & dilute to the mark with water.

Preparation of standard stock solution:[6000ppm Methanol, 10000ppm Acetone, 10000ppm Isopropyl Alcohol and 1200ppm Dichloromethane]

Weigh accurately 600mg of methanol, 1000mg of Acetone, 1000mg of Isopropyl alcohol and 120mg of dichloromethane in 100 ml volumetric flask containing 25ml of Dimethylsulfoxide & dilute to the mark with Dimethylsulfoxide.

Preparation of Standard solution: [300ppm Methanol, 500ppm Acetone, 500ppm Isopropyl alcohol and 60ppm Dichloromethane]

Pipette out 5 ml of Standard stock solution in 100 ml volumetric flask, mix & dilute to the mark with diluent.

Pipette out accurately 5 ml of the solution into an individual six vials fitted with a septum and crimp cap.

Preparation of Test solution: (Two time)

Weigh 500 mg of sample and dissolve in 5 ml of diluent.

Procedure: Inject the solution as per the sequence.

Sr. No.	Solutions	No. of Injections
01	Blank solution	01
02	Standard solution	06
03	Blank solution	01
04	Test solution-01	01
05	Test solution-01	01
06	Test solution-02	01
07	Blank solution	01
08	Bracketing Standard solution	01

Evaluation of system suitability:

a) Theoretical plates for each solvent should not less than 5000.

b) Resolution between each solvent should not be less than 1.5

c) Tailing factor for each solvent should not more than 1.5.

d) % RSD for peak area NMT 15.0% and for retention time NMT 2.0%.

Calculations:

$$\text{Methanol in ppm} = \frac{\text{Avg. peak area of methanol in test}}{\text{Avg. peak area of methanol in std.}} \times \frac{\text{Wt. of Std.}}{100} \times \frac{5}{100} \times \frac{5}{\text{Wt. of sample}} \times 1000000$$

$$\text{Acetone in ppm} = \frac{\text{Avg. peak area of acetone in test}}{\text{Avg. peak area of acetone in std.}} \times \frac{\text{Wt. of Std.}}{100} \times \frac{5}{100} \times \frac{5}{\text{Wt. of sample}} \times 1000000$$

$$\text{Isopropyl Alcohol in ppm} = \frac{\text{Avg. peak area of IPA in test}}{\text{Avg. peak area of IPA in std.}} \times \frac{\text{Wt. of Std.}}{100} \times \frac{5}{100} \times \frac{5}{\text{Wt. of sample}} \times 1000000$$

$$\text{Dichloromethane in ppm} = \frac{\text{Avg. peak area of MDC in test}}{\text{Avg. peak area of MDC in std.}} \times \frac{\text{Wt. of Std.}}{100} \times \frac{5}{100} \times \frac{5}{\text{Wt. of sample}} \times 1000000$$

Table-:Risk management summary table for Metal elements 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	Yes	Absent
V	2A	No	Yes	Absent
Ni	2A	No	Yes	Absent
Ti	2B	No	No	Not tested as per Table 5.1 of ICH Q3D for Oral drug
Au	2B	No	No	Not tested as per Table 5.1 of ICH Q3D for Oral drug
Pd	2B	No	No	Not tested as per Table 5.1 of ICH Q3D for Oral drug
Ir	2B	No	No	Not tested as per Table 5.1 of ICH Q3D for Oral drug
Os	2B	No	No	Not tested as per Table 5.1 of ICH Q3D for Oral drug
Rh	2B	No	No	Not tested as per Table 5.1 of ICH Q3D for Oral drug
Ru	2B	No	No	Not tested as per Table 5.1 of ICH Q3D for Oral drug

Intended route of administration / Use of the substance: Oral				
Element	**Class**	**Intentionally added?**	**Considered in risk management?**	**Conclusion**
Se	2B	No	No	Not tested as per Table 5.1 of ICH Q3D for Oral drug
Ag	2B	No	No	Not tested as per Table 5.1 of ICH Q3D for Oral drug
Pt	2B	No	No	Not tested as per Table 5.1 of ICH Q3D for Oral drug
Li	3	No	No	Not tested as per Table 5.1 of ICH Q3D for Oral drug
Sb	3	No	No	Not tested as per Table 5.1 of ICH Q3D for Oral drug
Ba	3	No	No	Not tested as per Table 5.1 of ICH Q3D for Oral drug
Mo	3	No	No	Not tested as per Table 5.1 of ICH Q3D for Oral drug
Cu	3	No	No	Not tested as per Table 5.1 of ICH Q3D for Oral drug
Sn	3	No	No	Not tested as per Table 5.1 of ICH Q3D for Oral drug
Cr	3	No	No	Not tested as per Table 5.1 of ICH Q3D for Oral drug

Note: Absent means Below 30% of permissible limit for oral dosage.