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 2011-328-Rev 02

Name of the substance:
METFORMIN HYDROCHLORIDE

Name of holder:
EXEMED PHARMACEUTICALS
Block No. 628 (A & B), ECP Canal Road
Village Luna, Taluka Padra
India-391 440 Vadodara, Gujarat

Site(s) of production:
SEE ANNEX 1

THIS CERTIFICATE SUPERSEDES THE PREVIOUS CERTIFICATE
R1-CEP 2011-328-REV 01

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 **METFORMIN HYDROCHLORIDE** no. 931 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)

Methanol	not more than 3000 ppm
Xylene	not more than 2170 ppm

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 5 years if stored in double polyethylene bags, placed in either a cardboard box or a fibre drum or 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 – 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 **5 April 2018** 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 7 pages and the third of 2 pages.

This certificate has:

lines.

On behalf of the
Director of EDQM

Strasbourg, 18 November 2019

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

EXEMED PHARMACEUTICALS, as holder of the certificate of suitability

R1-CEP 2011-328-Rev 02 for Metformin Hydrochloride

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
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Certification of Substances Department

Annex 1 : Site(s) of production for R1-CEP 2011-328-Rev 02

Production of Metformin Hydrochloride:
EXEMED PHARMACEUTICALS
Block No. 628 (A & B), ECP Canal Road
Village Luna, Taluka Padra
India-391 440 Vadodara, Gujarat

Residual Solvents:

Reagents:

Methanol (AR Grade)

Xylene (AR Grade)

1-Methyl 2-pyrrolidinone (Diluent) (AR Grade)

Chromatographic conditions:

Column: Fused silica capillary column DB-1, (30m x 0.32 mm, 1 µm)

Instrument parameters:

Make: Shimadzu GC2010 with Teledyne HT3 HS

GC Parameters Shimadzu GC2010

Carrier gas	:	Nitrogen
Initial oven temperature	:	55 °C
Initial hold time	:	5 minutes
Programming rate	:	15 °C / minutes
Final temperature	:	220 °C
Hold time	:	8 minutes
Flow rate	:	1.0 ml/min (4.9 psi)
Flow control mode	:	Pressure constant
Injection mode	:	Split
Split	:	On
Split Ratio	:	1 : 2
Injection temperature	:	180 °C
Detector	:	Flame Ionization
Detector temperature	:	230 °C
Hydrogen flow	:	40 ml / minute
Air flow	:	400 ml / minute
Make up gas	:	N_2/ Air
Make up flow	:	30 ml/ min

Head space parameters: Teledyne HT3

Heat time	:	Constant
Valve oven temperature	:	95 °C
Transfer line temperature	:	100 °C

Standby flow rate	:	70 ml / min
Platen / Sample temperature	:	75 °C
Platen temperature equilibration time	:	1 minute
Sample equilibration time	:	20 minutes
GC cycle time	:	30.0 minutes
Mixer	:	On
Mixer time	:	5.00 min
Mixer level	:	Level 5
Mixing Stabilize time	:	0.50 min
Pressurize	:	10 PSIG
Pressurize time	:	1.0 minutes
Pressure equilibration time	:	0.10 minute
Loop fill pressure	:	5 PSIG
Loop fill time	:	1 minute
Injection time	:	1.0 minute
Injection Volume	:	1.0 ml of gaseous phase.

Alternate / Equivalent instrument and method

Make: Agilent 7890B with Headspace G1888

GC Parameters:

Carrier Gas	:	Nitrogen
Initial oven temperature	:	55 °C
Initial hold time	:	5 minutes
Programming rate	:	15 °C / minutes

Final temperature	:	220 °C
Hold time	:	8 minutes
Constant Flow (Constant Pressure)	:	1.0 ml/min (4.9 psi)
Flow control mode	:	Constant Pressure
Injection mode	:	Split
Split	:	On
Split Ratio	:	1 : 50
Septum Purge flow	:	3.00 ml / min
Injection temperature	:	180 °C
Detector	:	Flame Ionization
Detector temperature	:	230 °C
Hydrogen flow	:	40 ml / minute
Air flow	:	400 ml / minute
Make up gas	:	N_2 / Air
Make up flow	:	30 ml/min

Head space parameters Agilent G1888:

Oven temperature	:	75 °C
Loop temperature	:	95 °C
Transfer line temperature	:	100 °C
Temperature Equilibration time	:	1.0 min
Vial size	:	20 ml
Shaking	:	Low
Vial equilibration time	:	20 minutes

GC cycle time	:	30.0 minutes
Pressurization Time	:	1.00 min
Pressurization Eq Time	:	0.10 min
Loop fill time	:	1.00 min
Loop Equilibration time	:	0.10 min
Sampler Inject time	:	1.00 min
Sequence Valve purge time	:	0.5 min

Diluent: 1-methyl-2-pyrrolidone used as a diluent.

Blank: Transfer 1 ml of diluent in headspace vial seals the vial using butyl rubber septa (Make single preparation).

Preparation of composite stock standard solution "S": Transferred about 25 ml of diluent into a 100 ml volumetric flask and tarred to zero. Weigh accurately about 300 mg of methanol standard and 217 mg of Xylene standard into the same 100 ml volumetric flask. Diluted to the volume with diluent and mix well. Designated this preparation as composite stock standard solution "S" contained about 3000 ppm of methanol and 2170 ppm of xylene.

Preparation of composite standard solution "S_1": Transferred accurately 5.0 ml of above composite stock standard solution "S" into a 50 ml volumetric flask. Diluted to the volume with diluent and mix well. Designated this preparation as composite standard solution "S_1" contained about 300 ppm of methanol and 217 ppm of xylene. Transfer accurately 1.0 ml of composite standard solution into a 20 ml head space vial. Applied Stoppard and capped to it.

Preparation of Test solution: Weigh accurately and transfer about 100 mg of metformin hydrochloride API into a 20 ml head space vial a head space vial. Added accurately 1.0 ml of diluent to it and mixed well. Applied Stoppard and capped to it. (Make two preparations separately)

Procedure: Place headspace vials of blank followed by composite standard solution in 6 vials separately and test preparation in duplicates on headspace magazine and run the GC and head space under above chromatographic conditions. Note down the area peaks of solvents in the chromatograms. Integrate the peaks of solvent in the sample and standard chromatogram.

Order of injections:

Sr. No.	Name of solution	No. of injections	Remarks	
1.	Diluent as a Blank	1	Identification of blank peaks in sample	
2.	Composite Standard solution	6	For system suitability and calculation	RSD ≤10.0%
3.	Test solution per one batch	2	Determination of solvent conc.	
4.	Bracketing standard solution	1	For system suitability	

Note: i) If more than 5 batches, one injection of Composite Standard solution shall be injected after every 5 batches (or 10 injections of test samples). Check RSD of areas of first six replicate injections of Standard solution and one after i.e. 7 standards is less than 10.0%.

ii) Individual residual solvents values from two different preparations should comply with the specifications. Calculate the mean value and report the same.

System suitability criteria:

- The relative standard deviation (% of RSD) for six replicate injections of composite standard preparation (peak area for each solvent) should be less than or equal to 10.0%
- The resolution between first peak of Xylene & second peak of Xylene should not be less than 1.2 in composite standard preparation.

Calculation:

Calculate amount in ppm of each residual solvent in individual vial by using the following formula and report the average.

For Xylene:

$$\text{Xylene [µg/g] or ppm} = \frac{Ru}{Rs} X \frac{Wstd}{100} X \frac{5}{50} X \frac{1}{W\ spl} X \frac{P}{100} X 10^6$$

Where,

Ru = Sum of peak areas of Xylene in the test solution chromatogram.

Rs = Sum of peak area of Xylene in standard solution chromatogram.

W std = Weight of Xylene standard in mg.

W spl = Weight of sample in mg.

P = Purity of Xylene solvent (as is basis)

For Methanol:

$$\text{Methanol [µg/g] or ppm} = \frac{Ru}{Rs} X \frac{Wstd}{100} X \frac{5}{50} X \frac{1}{W\ spl} X \frac{P}{100} X 10^6$$

Where,

Ru = Peak area of Methanol in the test solution chromatogram.

Rs = Peak area of Methanol in standard solution chromatogram.

W std = Weight of Methanol standard in mg.

W spl = Weight of sample in mg.

P = Purity of Methanol solvent (as is basis)

Calculate the amount of Methanol in individual vial and report the average.

LOD level: Xylene = 44 ppm, Methanol = 60 ppm

LOQ level: Xylene = 88 ppm, Methanol = 121 ppm

Note: Report results as a "BLQ" if obtained results are below LOQ level and as "BLD" if obtained results are below LOD level.

Elemental Impurities

The Intended route of administration for Metformin Hydrochloride is Oral, However we have considered stringent approach and tested drug substance with a stringent limit (Parenteral).

Risk management summary:

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
Tl	2B	No	No	NA
Au	2B	No	No	NA
Pd	2B	No	No	NA
Ir	2B	No	No	NA
Os	2B	No	No	NA
Rh	2B	No	No	NA
Ru	2B	No	No	NA
Se	2B	No	No	NA
Ag	2B	No	No	NA
Pt	2B	No	No	NA

Element	Class	Intentionally added?	Considered in Risk management?	Conclusion*
Li	3	No	No	NA
Sb	3	No	No	NA
Ba	3	No	No	NA
Mo	3	No	No	NA
Cu	3	No	No	NA
Sn	3	No	No	NA
Cr	3	No	No	NA

"Absent" (meaning less than 30% of ICH Q3D option 1 limit).