Certification of Substances Department

Certificate of suitability
No. R1-CEP 2012-285 - Rev 01

Name of the substance:
TIOTROPIUM BROMIDE MONOHYDRATE
Micronised, non-micronised

Name of holder:
VAMSI LABS LIMITED
A-14, A-15, A-31, A-32 and A-33, M.I.D.C. Area
Chincholi
India-413 255 Solapur, Maharashtra

Site(s) of production:
SEE ANNEX 1

THIS CERTIFICATE SUPERSEDES THE PREVIOUS CERTIFICATE
R1-CEP 2012-285 - 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 **TIOTROPIUM BROMIDE MONOHYDRATE** no. 2420 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 5000 ppm

In the last steps of the synthesis water is used as solvent.

No elemental impurity classified in ICH Q3D is intentionally introduced in the manufacture of the substance.

– Test for particle size by laser diffraction (Annex 3)
Micronised:
95% of particles less than 5 µm
97% of particles less than 10 µm
Non-micronised:
95% of particles less than 1000 µm
97% of particles less than 1200 µm

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

The re-test period of the substance is 12 months if stored under nitrogen in a double polyethylene bag (outer black) 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.

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 **21 November 2019** 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, 28 July 2022

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

Vamsi Labs Limited, as holder of the certificate of suitability

R1-CEP 2012-285 - Rev 01 for Tiotropium bromide monohydrate

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

COUNCIL OF EUROPE
CONSEIL DE L'EUROPE

Certification of Substances Department

Annex 1: Site(s) of production for R1-CEP 2012-285 - Rev 01

Production of Tiotropium bromide monohydrate:

VAMSI LABS LIMITED
A-14, A-15, A-31, A-32 and A-33, M.I.D.C. Area
Chincholi
India-413 255 Solapur, Maharashtra

3.0	Standard Testing Procedure and additional method	
3.9	Residual solvent by GC headspace. * In-house test	
3.9.1	Equipment	GC HS, Younglin, GC-1600, with FID and head space Auto injector, Data handling system.
	Column	DB-624, (6% Cynopropylphenyl and 94%dimethyl polysiloxane) 30 m x 0.53 mm ID, 3.00 µm or equivalent.
	Name of the detector	FID (Flame-ionization detector)
	Carrier Gas	Nitrogen for chromatography.
	Injection system	Auto
	Chemical /reagents	Make
	Dimethyl Sulfoxide	Sd Fine- Chem
	Acetone	Sd Fine- Chem
	Toluene	Sd Fine- Chem
	Acetonitrile	Sd Fine- Chem
	Methylene dichloride	Sd Fine- Chem
	Ethanol	Sd Fine- Chem
	n-Hexane	Sd Fine- Chem
	Methanol	Sd Fine-Chem
	Benzene	Sd Fine-Chem
	Diethyl Ether	Sd Fine-Chem
	Tetrahydrofuran	Sd Fine-Chem
	O-Xylene	Sd Fine-Chem
	Isopropyl alcohol	Sd Fine-Chem
	Chromatographic condition	
	Initial oven temperature	48°C
	Initial time	10 min
	Rate	15°C/min
	Final oven temperature	250°C
	Final time	2 min

3.0	Standard Testing Procedure and additional method		
	Sr. No	Test	Specification
		Injector temperature	200°C
		FID Temperature (1)	250°C
		Carrier Gas (N_2) Flow	3.0 mL/min
		Split flow	30 mL/min
		Split	10:1
	3.9.2	Headspace parameters	
		Vial Oven temperature	50°C
		Loop temperature	60°C
		Transfer line temperature	70°C
		Vial Equilibrium	12.0 min.
		Pressurization	0.2 min.
		Loop fill	0.2 min.
		Loop equilibrium	0.02 min.
		Injection time	0.50 min
		Diluent	DMSO
		Injection volume	1000 micro lts
		Max. GC Cycle time	37.0 min (Run + Post run + Cooling + Prep run)
		Diluent	DMSO
	3.9.3	Preparation of blank solution	Transfer 5 mL of diluent to a headspace vial and seal the vial immediately.
	3.9.4	Preparation of standard stock solution (A)	Accurately weigh about 0.60 g Methanol, 1.0 g Ethanol, 1.0 g of Acetone, 1.0 g of Isopropyl alcohol, 0.082 g of Acetonitrile, 0.1780 g of Toluene, 0.1200 g of Methylene dichloride and 0.0580 g n-hexane ,1.0 g of Diethyl ether,0.1440 g of Tetrahydrofuran, 0.4340 g of O-xylene in 100 ml volumetric Flask containing about 10 ml of diluents. Make up the volume with diluents.
	3.9.5	Preparation of standard stock solution (B)	Accurately weigh about 0.0500 g of benzene in 25 ml of DMSO. Take 1 ml of this solution and dilute with 100 ml of DMSO.
	3.9.6	Preparation of standard solution	Take 10 ml of standard stock solution (A) and 2.0 ml of standard stock solution (B) in 100 ml of DMSO.
	3.9.7	Preparation of sample	Accurately weigh and transfer about 1.0 g of sample to the headspace vial adds 5.0 mL of diluent and seal the vial immediately.
	3.9.8	Evaluation of blank solution	Place the sealed vial of the blank solution in the magazine and run the headspace. No peak should be observed at the retention time of analyte.

3.0	Standard Testing Procedure and additional method		
	Sr. No.	Test	Specification
	3.9.9	Evaluation of system suitability	Inject the standard solution into the chromatograph using above chromatographic parameters and note the peak areas of eluting peaks from the chromatographic report. The system is suitable for analysis, if and only if; the relative standard deviation of area counts of six replicate injections for all solvents is not more than 15.0%. Precaution to be taken during analysis Heat the column at 240°C for half an hour before starting the analysis.
	3.9.10	Injection sequence	Diluent blank : 01 Standard solution-06 Sample solution -01

3.0	Standard Testing Procedure and additional method

3.10	Particle Size *	In house test (Micronised grade)
3.10.1	Sample preparation:	Mix the sample properly and transfer about 1 gm of the sample, with the aid of a dry spatula into the sample feeder. Set the software parameters as specified under "Typical conditions"
3.10.2	Method	Malvern Mastersizer 2000Parameters
3.10.3	Instrument and Software	Malvern Mastersizer– 2000 Ver. 5.60
3.10.4	Accessory	Malvern Scirocco 2000
3.10.5	Size Range	0.020 µm to 2000 µm
3.10.6	Dispersant	Air
3.10.7	Particle (Material) Refractive Index	1.52
3.10.8	Dispersant (Air) Refractive Index	1.0
3.10.9	Absorption	0.1
3.10.10	Analysis Model	General Purpose
3.10.11	Sensitivity	Normal

3.0	Standard Testing Procedure and additional method		
	Sr. No	Test	Specification
	3.10.12	Background time	10sec.
	3.10.13	Measurement	04 sec.
	3.10.14	Air pressure	2.0 bar
	3.10.15	Vibration feed rate	40 %
	3.10.16	Obscuration	0.5% to 5.0%
	3.10.17	Measurement Sequence	1
	3.10.18	Replicate(s)	3
	3.11	Particle Size *	In house test (Non-Micronised grade)
	3.11.1	Sample preparation:	Mix the sample properly and transfer about 1 gm of the sample, with the aid of a dry spatula into the sample feeder. Set the software parameters as specified under "Typical conditions"
	3.11.2	Method	Malvern Mastersizer 2000Parameters
	3.11.3	Instrument and Software	Malvern Mastersizer– 2000 Ver. 5.60
	3.11.4	Accessory	Malvern Scirocco 2000
	3.11.5	Size Range	0.020 µm to 2000 µm
	3.11.6	Dispersant	Air
	3.11.7	Particle (Material) Refractive Index	1.52
	3.11.8	Dispersant (Air) Refractive Index	1.0
	3.11.9	Absorption	0.1
	3.11.10	Analysis Model	General Purpose
	3.11.11	Sensitivity	Normal
	3.11.12	Background time	10sec.
	3.11.13	Measurement	04 sec.
	3.11.14	Air pressure	2.0 bar
	3.11.15	Vibration feed rate	40 %
	3.11.16	Obscuration	0.5% to 5.0%
	3.11.17	Measurement Sequence	1
	3.11.18	Replicate(s)	3