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 2006-226 - Rev 02

Name of the substance:
SALMETEROL XINAFOATE
Non-micronised and 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 2006-226 - 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 **SALMETEROL XINAFOATE** no. 1765 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.

- Tests for residual solvents by gas chromatography

Acetone	not more than 5000 ppm	(Annex 2)
Methanol	not more than 3000 ppm	
Diethyl ether	not more than 5000 ppm	
Ethyl acetate	not more than 5000 ppm	
Ethylene dichloride	not more than 5 ppm	(Annex 3)

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

The following elemental impurities classified in ICH Q3D are intentionally introduced in the manufacture of the substance: Lithium and Palladium.

- Tests for particle size by laser diffraction

Non-micronised grade		(Annex 4)
95% of particles	not more than 250 µm	
97% of particles	not more than 300 µm	
Micronised grade		(Annex 5)
95% of particles	not more than 5 µm	
97% of particles	not more than 10 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 4 years if stored under nitrogen 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.

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 **1 June 2016** 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 five annexes, the first of 1 page, the second of 3 pages, the third of 2 pages, the fourth and the fifth of 1 page each.
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 2006-226 - Rev 02 for Salmeterol xinafoate

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*):

Certification of Substances Department

Annex 1: Site(s) of production for R1-CEP 2006-226 - Rev 02

Production of intermediate(s):

JAYANT SPECIALITIES PVT. LTD.
Plot No. K-21/22, M.I.D.C. Tarapur
Palghar District
India-401 506 Boisar, Maharashtra

Production of Salmeterol xinafoate:

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				
	Sr. No.	Test	Specification		
	3.7.*	Additional Test for Residual solvents by GC HS method*			
	3.7.1	Equipment	GC-Headspace.		
	3.7.2	Column	DB-624 (6 % cyanopropylphenyl and 94 % Dimethylpolysiloxane) 30 m x 0.53 mm ID, 3.00 µm or Equivalent.		
	3.7.3	Reagents	Dimethyl sulfoxide	SD fine chem.	AR grade
			Methanol	SD fine chem.	AR grade
			Diethyl Ether	SD fine chem.	AR grade
			Acetone	SD fine chem.	AR grade
			Methylene dichloride	SD fine chem.	AR grade
			Ethyl Acetate	SD fine chem.	AR grade
			Tetrahydrofuran	SD fine chem.	AR grade

3.0	Standard Testing Procedure and additional method				
	Sr. No.	Test	Specification		
			Toluene	SD fine chem.	AR grade
			Benzene	SD fine chem.	AR grade
			Chlorobenzene	SD fine chem.	AR grade
	3.7.4	Chromatographic conditions			
	3.7.4.1	Initial oven temp.	50°C		
	3.7.4.2	Initial Time	10 min.		
	3.7.4.3	Rate	15°C/ min.		
	3.7.4.4	Final oven temperature	250°C		
	3.7.4.5	Final Time	2 min.		
	3.7.4.6	Injector temperature	250°C		
	3.7.4.7	FID temperature (1)	270°C		
	3.7.4.8	Carrier Gas (N_2) Flow	3.0 mL/min +/- 0.25 mL/min		
	3.7.4.9	Split	5:1		
	3.7.5	Headspace parameter			
	3.7.5.1	Vial Oven temperature	80°C		
	3.7.5.2	Loop temperature	90°C		
	3.7.5.3	Transfer line temperature	100°C		
	3.7.5.4	Vial Equilibrium	12.0 min.		
	3.7.5.5	Pressurization	0.20 min.		
	3.7.5.6	Loop fill	0.20 min.		
	3.7.5.7	Loop Equilibrium	0.02 min.		
	3.7.5.8	Inject	0.50 min.		
	3.7.5.9	Maximum cycle time	35.0 min. (Run + Post run +cooling + Prep run)		
	3.7.6	Preparation of blank solution	Transfer 5 mL of diluent to a headspace vial and seal the vial immediately.		

3.0	Standard Testing Procedure and additional method		
	Sr. No.	Test	Specification
	3.7.7	Preparation of standard stock solution (A)	Accurately weigh about 0.60 g of Methanol, 1.0 g of Diethyl ether, 1.0 g of Acetone, 1.0 g of Ethyl Acetate, 0.178 g of Toluene, and 0.144 g of Tetra hydro furan, 1.0 g of Methylene dichloride and 0.07 g of chlorobenzene in a 100 mL volumetric flask containing about 10 mL of diluent. Makeup the volume with diluent.
	3.7.8	Preparation of standard stock solution (B)	Accurately weigh about 0.05 g of benzene in 25 ml of DMSO. Take 1 ml of this solution and dilute with 100 ml of DMSO.
	3.7.9	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.
	3.7.10	Preparation of sample	Take 1 g of sample and dissolve in 5 ml of DMSO.
	3.7.11	Evaluation of blank	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.
	3.7.12	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.
	3.7.13	Injection sequence	Diluent Blank-1 , Standard solution – 6, Sample each batch -1
	3.7.14	Calculation	
		$\text{Solvent in ppm} = \frac{AT}{AS} \times \frac{DS}{DT} \times 10^6$ Where, AT= Peak area counts of benzene in the chromatogram of the sample solution. AS= Average peak area counts of solvent which is used in the chromatograms of the standard Solution as obtained under system suitability. DT= Dilution factor of sample solution. DS= Dilution factor of standard solution.	

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3.0	Standard Testing Procedure and additional method		
	Sr. No.	Test	Specification
	3.10*	Residual solvent of Ethylene dichloride by GC HS method [In house method]*	
	3.10.1	Instrument	Gas chromatograph (Agilent 7890-B) with Flame ionization detector, with head space Auto injector, EZ-CHROME Data handling system.
	3.10.2	Column	DB-624(6 % cyanopropylphenyl and 94 % Dimethyl polysiloxane) 30 m x 0.53 mm ID, 3.00 µm
	3.10.3	Chromatographic Conditions:	
		Initial oven temperature	50°C
		Initial time	5 min
		Rate	12°C/min
		Final time	0 min
		Injector temperature	250°C
		FID Temperature	270°C
		Carrier Gas (N_2) Flow	3.0 ml/min
		Split	2:1
	3.10.4	Head Space Parameter	
		Oven temperature	80°C
		Loop temperature	90°C
		Transfer line	100°C
		Vial Equilibrium	12 min
		Inject time	1.0 min
		Maximum GC Cycle	31 Min. (Run+ Post Run+ Cooling + Prep Run)
		Injection volume	1.0 ml
	3.10.5	Preparation of Blank (White)	Transfer 5 ml of diluent to a headspace vial and seal the vial immediately.
	3.10.6	Preparation of EDC standard stock solution	Weigh about 0.05074 g of Ethylene dichloride, in a 25 ml volumetric flask containing about 10 mL of diluent. Makeup the volume with diluents. Dilute 1 ml of this solution diluted to 100 ml with Diluents.

3.0	Standard Testing Procedure and additional method		
	Sr. No.	Test	Specification
	3.10.7	Preparation of standard solution	Dilute 5 ml of standard stock solution to 100 ml of Diluents.
	3.10.8	Sample preparation	Accurately weigh and transfer about 1.00027 g of sample to the Headspace vial adds 5 ml of diluent and seal the vial immediately.
	3.10.9	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%.
	3.10.10	Injection sequence	Diluent Blank-1 , Standard solution – 6, Sample each batch -1
	3.10.11	Calculation	
		Calculated the content of each residual solvent (in ppm) by using the following formula: $= \frac{r_U}{r_S} \times \frac{C_S}{C_U} \times 1000000$ r_U: Peak response of solvent from the sample solution. r_S: Peak response of solvent from the standard solution. C_S: Concentration of standard solution. C_U: Concentration of sample solution.	

* Validated in-house test procedure.

3.0	Standard Testing Procedure and additional method		
	Sr. No.	Test	Specification
	3.9*	PSD testing method for in-house Non-Micronised samples (Malvern analyzer) [In house method]*	
	3.9.1	Malvern Mastersizer 2000Parameters	Method
	3.9.2	Instrument and Software	Malvern Mastersizer– 2000 Ver. 5.60
	3.9.3	Accessory	Malvern Scirocco 2000
	3.9.4	Size Range	0.020 µm to 2000 µm
	3.9.5	Dispersant	Air
	3.9.6	Particle (Material)Refractive Index	1.52
	3.9.7	Dispersant (Air)Refractive Index	1.0
	3.9.8	Absorption	0.1
	3.9.9	Analysis Model	General Purpose
	3.9.10	Sensitivity	Normal
	3.9.11	Background time	10 sec.
	3.9.12	Measurement	10 sec.
	3.9.13	Air pressure	1.5 bar
	3.9.14	Vibration feed rate	40 %
	3.9.15	Sample preparation	Mix the sample properly and transfer about 1 gm of the sample, with the add of dry spatula in to the sample feeder. Set the software parameters as specified under "Typical Conditions".
	3.9.16	Obscuration	0.5% to 5.0%
	3.9.17	Measurement Sequence	1
	3.9.18	Replicate(s)	3

* Validated in-house test procedure.