

Certification of Substances Department

Vamsi Labs Limited

Mr Govardhan ADAM
Plot No. A-14/15, M.I.D.C. Area
Chincholi
India-413 255 Solapur, Maharashtra

CEP_RZ_PH_2006-226-1216619

Strasbourg, 5 June 2019

RVZ/vme

Re: R1-CEP 2006-226-Rev 01/Salmeterol xinafoate Non-micronised and micronised

Dear Mr ADAM,

Please find enclosed the revised certificate granted for **Salmeterol xinafoate** following the evaluation of the dossier.

If you find a mistake on the CEP, you should notify EDQM within 3 months. After this deadline, any complaint will no longer be considered valid.

Please note that a copy of this certificate has to be sent to your customers and/or any relevant competent authority to allow them to update their documentation and in particular the relevant marketing authorisations for medicinal products.

Yours faithfully,

Radu-Virgil ZAHARIA
Scientific Assistant

H el ene BRUGUERA
Head of Department

Certification of Substances Department

Certificate of suitability
No. R1-CEP 2006-226-Rev 01

1 *Name of the substance:*

2 **SALMETEROL XINAFOATE**

3 Non-micronised and micronised

4 *Name of holder:*

5 **VAMSI LABS LIMITED**

6 Plot No. A-14/15, M.I.D.C. Area

7 Chincholi

8 India-413 255 Solapur, Maharashtra

9 *Site(s) of production:*

10 **SEE ANNEX 1**

11 **THIS CERTIFICATE SUPERSEDES THE PREVIOUS CERTIFICATE**

12 **R1-CEP 2006-226-REV 00**

13 After examination of the information provided on the manufacturing method and subsequent processes
14 (including purification) for this substance on the site(s) of production listed in annex, we certify that the
15 quality of the substance is suitably controlled by the current version of the monograph **SALMETEROL**
16 **XINAFOATE** no. 1765 of the European Pharmacopoeia, current edition including supplements, only if it
17 is supplemented by the test(s) mentioned below, based on the analytical procedure(s) given in annex.

18 – Tests for residual solvents by gas chromatography

19 Acetone not more than 5000 ppm (Annex 2)

20 Methanol not more than 3000 ppm

21 Diethyl ether not more than 5000 ppm

22 Ethyl acetate not more than 5000 ppm

23 Ethylene dichloride not more than 5 ppm (Annex 3)

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

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

27 – Tests for particle size by laser diffraction

28 Non-micronised grade (Annex 4)

29 95% of particles not more than 250 µm

30 97% of particles not more than 300 µm

31 Micronised grade (Annex 5)

32 95% of particles not more than 5 µm

33 97% of particles not more than 10 µm

34 The re-test period of the substance is 4 years if stored under nitrogen in double polyethylene bags
35 placed in a polyethylene drum.

36 The holder of the certificate has declared the absence of use of material of human or animal origin
37 in the manufacture of the substance.

38 The submitted dossier must be updated after any significant change that may alter the quality, safety
39 or efficacy of the substance.


40 Manufacture of the substance shall take place in accordance with the Good Manufacturing Practice and
41 in accordance with the dossier submitted.

42 Failure to comply with these provisions will render this certificate void.

43 This certificate is renewed from **1 June 2016** according to the provisions of Resolution AP-CSP (07) 1,
44 and of Directive 2001/83/EC and Directive 2001/82/EC and any subsequent amendment, and the
45 related guidelines.

46 This certificate has five annexes, the first of 1 page, the second of 3 pages, the third of 2 pages and
47 the fourth and the fifth of 1 page each.

48 This certificate has:
49 lines.


On behalf of the
Director of EDQM



Strasbourg, 5 June 2019

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 01 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)*:

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 2006-226-Rev 01

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
Plot No. A-14/15, M.I.D.C. Area
Chincholi
India-413 255 Solapur, Maharashtra



Vamsi Labs Ltd.

Salmeterol Xinafoate Micronised. Current specification
(Module 3-Quality: Renewal/Revision)

M3- 249

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



 Vamsi Labs Ltd.	Salmeterol Xinafoate Micronised. (Module 3-Quality: Renewal/Revision)	Current specification M3- 250
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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.	



 Vamsi Labs Ltd.	Salmeterol Xinafoate Micronised. Current specification (Module 3-Quality: Renewal/Revision)	M3- 251
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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	
$\text{Solvent in ppm} = \frac{AT}{AS} \times \frac{DS}{DT} \times 10^6$ <p>Where,</p> <p>AT= Peak area counts of benzene in the chromatogram of the sample solution.</p> <p>AS= Average peak area counts of solvent which is used in the chromatograms of the standard Solution as obtained under system suitability.</p> <p>DT= Dilution factor of sample solution.</p> <p>DS= Dilution factor of standard solution.</p>		





Vamsi Labs
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Salmeterol Xinafoate (Non micronised and Micronised)
Current specification
(REVISION- Module 3: Quality)

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.





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Salmeterol Xinafoate (Non micronised and Micronised)
Current specification
(REVISION- Module 3: Quality)

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.





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Salmeterol Xinafoate Micronised. Current specification
(Module 3-Quality: Renewal/Revision)

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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.





Vamsi Labs Ltd.

Salmeterol Xinafoate Micronised. Current specification
(Module 3-Quality: Renewal/Revision)

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3.0 Standard Testing Procedure and additional method		
Sr. No.	Test	Specification
3.8*	PSD testing method for in-house Micronised samples (Malvern analyzer) [In house method]*	
3.8.1	Malvern Mastersizer 2000 Parameters	Method
3.8.2	Instrument and Software	Malvern Mastersizer – 2000 Ver. 5.60
3.8.3	Dispersion	Malvern Hydro 2000S
3.8.4	Size Range	0.020µm to 2000 µm
3.8.5	Dispersant	Purified Water or HPLC water
3.8.6	Particle (Material)Refractive Index	1.565
3.8.7	Dispersant Refractive Index	1.33
3.8.8	Absorption	0.1
3.8.10	Model Analysis	General Purpose
3.8.11	Sensitivity	Normal
3.8.12	Stirrer Speed	3000 RPM
3.8.13	Background time	10s
3.8.14	Measurement	10s
3.8.15	Preparation of 2 %Tween 80 soln	1 ml tween 80 to 50 ml water (2% w/v)
3.8.16	Sample preparation	Transfer about 100 mg sample into 100 ml beaker. Add 2 ml of tween 80 (2%) solution and make slurry with glass rod. Add 20 ml of water to it. After that sonicate for 1 minute and make sure that there are no lumps in the solution.
3.8.17	<u>Precaution</u>	Note that after sonication air bubbles may form at the top of the solution. Remove the bubbles by glass rod. Then perform the analysis.
3.8.18	Ultrasound	50 % for 3 min.
3.8.19	Obscuration	10% to 30%
3.8.20	Measurement Sequence	3 run
3.8.21	Replicate(s)	3

