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. R0-CEP 2020-160 - Rev 01

Name of the substance:
FENOTEROL HYDROBROMIDE

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
R0-CEP 2020-160 - 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 **FENOTEROL HYDROBROMIDE** no. 901 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
Dichloromethane	not more than 600 ppm

In the last steps of the synthesis isopropanol and water are used as solvents. Their residual content is limited by the test for loss on drying described in the monograph with a limit of not more than 0.5%.

The following elemental impurity classified in ICH Q3D is intentionally introduced in the manufacture of the substance: Palladium.

– Test for elemental impurities by ICP-MS (Annex 3)

Palladium	not more than 0.1 ppm

The re-test period of the substance is 36 months in double polyethylene bags (outer black), placed in a polyethylene drum.

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 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 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 **8 March 2022**. 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 and the third of 4 pages 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

R0-CEP 2020-160 - Rev 01 for Fenoterol hydrobromide

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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CONSEIL DE L'EUROPE

Certification of Substances Department

Annex 1: Site(s) of production for R0-CEP 2020-160 - Rev 01

Production of Fenoterol hydrobromide:

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

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Sr. No.	Standard testing procedure	Reference No.
	Ensure that flames are not produced at any time during the procedure. Allow the crucible to cool in desiccators over silica gel or other suitable desiccant, weigh it again and Calculate the percentage of residue. If the amount of the residue so obtained exceeds the prescribed limit, repeat the moistening with sulfuric acid and ignition, as previously, for 30 min. periods until 2 consecutive weights do not differ by more than 0.5 mg or until the percentage of residue complies with the prescribed limit. The amount of substance used for the test (usually 1.2 g) is chosen so that at the prescribed limit the mass of the residue (usually about 1 mg) can be measured with sufficient accuracy. Calculation: $\text{Sulfated ash} = \frac{W3 - W1}{W2 - W1} \times 100$	
10.0	Assay :	EP
10.1	Dissolve 0.600 gm in 50 ml of water R and add 5 ml of dilute nitric acid R, 25.0 ml of 0.1 M silver nitrate and 2 ml of ferric ammonium sulfate solution R2. Shake and titrate with 0.1 M ammonium thiocyanate until an orange colour is obtained. Carry out a blank titration. 1 ml of 0.1 M Silver Nitrate is equivalent to 38.43 mg of $C_{17}H_{22}BrNO4$.	Sample Quantity 0.600 gm
11.0	Residual solvent by GC Head space:	In-House
11.1	Reagents and Chemicals: Isopropyl alcohol NMT 5000 ppm Methanol NMT 3000 ppm Toluene NMT 890 ppm Methylene chloride NMT 600 ppm Ethanol NMT 5000 ppm Benzene NMT 02 ppm	

Sr. No.	Standard testing procedure	Reference No.
11.2	Column: DB-624, (6% Cynopropylphenyl and 94 % Dimethylpolysiloxane) 30 m x 0.53 mm ID, 3.00 µm or Equivalent. Name of detector : FID (Flame-ionization detector) Injection system : Auto Carrier gas : Nitrogen for chromatography. Instrument Parameters Initial oven temperature : 35°C Initial time : 10 min. Rate : 15°C/min. Final Oven temperature : 240°C Final time : 2 min Injector temperature : 225°C Split ratio : 2:1 FID temperature : 250°C Carrier gas (N2) flow : 3.0 ml/min Head Space Parameters Vial oven temperature : 80°C Loop temperature : 90°C Transfer line temperature : 100°C Injection time : 1.00 min. Vial Equilibration time : 12 min. GC Cycle time : 37 min. (Run + Post Run + Cooling + Prep Run) Diluent : DMSO Injection Volume : 1000 µl. Note: Purity of diluent used in the analysis should be checked for any impurities eluting at the same RT as that of the different residual solvents analyzed by this method.	

FENOTEROL HYDROBROMIDE - EP

Sr. No.	Standard testing procedure	Reference No.
11.3	Preparation of blank solution: Transfer 5 ml of diluent to a headspace vial and seal the vial immediately.	
11.4	Preparation of standard stock solution: Accurately weigh about 0.60 g Methanol, 1.0 g of Ethanol, 1.0 g Isopropyl alcohol, 0.178 g of Toluene, 0.12 g Methylene dichloride, in 100 ml volumetric flask containing about 10 ml of diluent. Make up the volume with diluent.	
11.5	Preparation of Benzene stock solution: Accurately weigh about 0.05 g of benzene stock solution in a 25 ml volumetric flask containing about 10 ml of diluent and make up the volume with diluent. Dilute 1.0 ml of this solution to 100 ml with diluent.	
11.6	Preparation of standard solution: Dilute 10 ml of standard stock solution and 2 ml of benzene stock solution diluted to 100 ml of diluent.	
11.7	Preparation of sample solution: Accurately weigh and transfer about 1.0 g of sample to the headspace vial and add 5.0 ml of diluent and seal the vial immediately	
11.8	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.	
11.9	System Suitability : Inject the standard solution in to 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 RSD of area of six replicate injections for all solvents is not more than 15.0 % & Retention time NMT 2.0 %.Precaution to be taken during analysis, Heat the column at 240°C for half an hour before starting the analysis.	

<table>
<tr><th>Sr. No.</th><th>Standard testing procedure</th><th>Reference No.</th></tr>
<tr><td>11.10</td><td>Injection sequence:
<table>
<tr><th>Sr. No.</th><th>Sample information</th><th>No. of injections</th></tr>
<tr><td>1.</td><td>Diluent Blank</td><td>01</td></tr>
<tr><td>2.</td><td>Standard solution</td><td>06</td></tr>
<tr><td>3.</td><td>Diluent blank</td><td>01</td></tr>
<tr><td>4.</td><td>Sample solution</td><td>01</td></tr>
</table></td><td></td></tr>
<tr><td>11.11</td><td>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 each solvent from the sample solution.
r_S: Peak response of each solvent from the standard solution.
C_S: Concentration of standard solution.
C_U: Concentration of sample solution</td><td></td></tr>
</table>

FENOTEROL HYDROBROMIDE - EP

Sr. No.	Standard testing procedure	Reference No.
12	Palladium Content: Not more than 0.1 PPM (By ICP-MS)	External Lab
	Instrument Parameters:	
	RF Power : 1550 W	
	Plasma gas flow (L/min) : 15.0	
	Nebulizer pump speed : 0.1 rps	
	Carrier Gas : Argon	
	Helium gas flow (mL/min) 4.3	
	Mode : He	
	Nebulizer Gas flow(L/min) : 1.05	
	Number of Replicates 3	
	Cone Nickel	
	Sample depth : 8.0 mm	
	Spray chamber temperature : 2°C	
	Integration Time/Mass : 0.9999 sec	
	Stabilization time : 10 sec	
	Acquisition Parameters	
	Acquisition Mode: Spectrum	
	Peak Pattern : 3 Points	
	Sweeps/Replicate : 100	
	Peri Pump (Sample Acquisition) Pre Run:	
	Sample Uptake Time: 40 sec	
	Uptake speed (Nebulizer pump) : 0.3 rps	
	Stabilise time: 45 sec	
	Uptake speed (Nebulizer pump) : 0.3 rps	
	Post Run:	
	Rinse speed (Nebulizer pump): 0.3 rps	
	Rinse at rinse vial (step-1): (40 sec) diluent.	
	Rinse at rinse Port (step-1): (10 sec)	

Sr. No.	Standard testing procedure	Reference No.
	Rinse speed (Nebulizer Pump) 0.3 rps	
	Rinse at Rinse Vail (Step-2) (10 Sec) 2% HNO_3	
	Rinse at Rinse Port (Step-2) (30 Sec)	
	Note: The above tuning parameters and instrument conditions may vary depending upon the instrument sensitivity/hardware changes to meet the acceptance criteria. Depending on the sample introduction tube length, uptake time and rinse time can be varied.	
	Preparation of Diluent: 3% HNO_3 (v/v)+ 1% HCL (v/v) Transferred 30 mL of Concentric acid and 10 mL of Conc.Hydrochloric acid in to 1000 mL volumetric flask containing 200 mL of Milli Q water, made up to the volume with Milli Q water.	
	Preparation of Standard Stock Solution-A: Transferred 0.5 mL of Pd, of 1000 ppm standard solutions into a 10 mL PP tube made-up to the volume with diluent.	
	Preparation of Standard Stock Solution-B: Transferred 1.0 mL of above standard stock solution-A, solution into a 10 mL PP tube made-up to the volume with diluent.	
	Preparation of Standard Stock Solution-C: Transferred 1.0 mL of standard stock solution-B, standard solution into a 10 mL PP tube made up to the mark with diluent	
	Preparation of Standard Stock Solution-D: Transferred 1.0 mL of standard stock solution-C, solution into a 10 mL PP tube made-up to the mark with diluent.	
	Preparation of Indium Internal standard :(10 ppm) Transferred 0.5 mL of 1000 ppm Indium standard solution in to 50 mL PP tube and made-up to the mark with diluent.	

FENOTEROL HYDROBROMIDE - EP

Sr. No.	Standard testing procedure	Reference No.
	Preparation of Indium Internal standard :(1 ppm) Transferred 5.0 mL of 10 ppm Indium standard solution in to 50 mL pp tube, and made up to the mark with diluent.	
	Calibration standard-1 (25%): Transferred 0.3 mL of standard stock solution–D, 0.2 mL of 1 ppm internal standard solution, 0.2 mL of Thiourea, 0.2 mL of L-Ascorbic acid solution and 0.1 mL of IPA in to 10 mL PP tube made up volume with diluent.	
	Calibration standard-2 (50%): Transferred 0.5 mL of standard stock solution–D, 0.2 mL of 1 ppm internal standard solution, 0.2 mL of Thiourea, 0.2 mL of L-Ascorbic acid solution and 0.1 mL of IPA in to 10 mL PP tube made up volume with diluent.	
	Calibration standard-3 (100%) Transferred 1.0 mL of standard stock solution–D, 0.2 mL of 1 ppm internal standard solution, 0.2 mL of Thiourea, 0.2 mL of L-Ascorbic acid solution and 0.1 mL of IPA in to 10 mL PP tube made up volume with diluent.	
	Calibration standard-4 (150%) Transferred 1.5 mL of standard stock solution–D, 0.2 mL of 1 ppm internal standard solution, 0.2 mL of Thiourea, 0.2 mL of L-Ascorbic acid solution and 0.1 mL of IPA in to 10 mL PP tube made up volume with diluent.	
	Calibration standard-5 (200%) Transferred 2.0 mL of standard stock solution–D, 0.2 mL of 1 ppm internal standard solution, 0.2 mL of Thiourea, 0.2 mL of L-Ascorbic acid solution and 0.1 mL of IPA in to 10 mL PP tube made up volume with diluent.	

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Sr. No.	Standard testing procedure	Reference No.
	Preparation of Sample Solution: Weigh 0.5 g of sample transfer into a 10 mL volumetric flask/ PP tube, add 6.0 mL of Diluent and add 0.2 mL of 1 ppm internal standard solution, shake up to dissolve and sonicate 30 min after completion of sonication add 0.2 mL of Thiourea solution and 0.2 mL of L-Ascorbic acid solution.1.0 mL of gold solution and 0.1 mL of IPA, make up to the mark with of Diluent and aspirate in to ICP-MS.	
	Preparation of Blank Solution: Prepare as same as sample preparation without sample.	