**Certification of Substances Department**

# Certificate of suitability
# No. R0-CEP 2020-078 - Rev 01

*Name of the substance:*
**FLUTICASONE PROPIONATE**
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**
**R0-CEP 2020-078 - 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 **FLUTICASONE PROPIONATE** no. 1750 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

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 light diffraction (Annex 3)
95% of the particles less than 5 µm
97% of the particles less than 10 µm

The substance is packed in four polyethylene bags (outer black) placed in a polyethylene container.

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F-67081 Strasbourg (France)
Tel: +33 (0) 3 88 41 30 30 – e-mail: cep@edqm.eu
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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 **29 October 2021**. 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 of 4 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

**R0-CEP 2020-078 - Rev 01 for Fluticasone propionate**

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 R0-CEP 2020-078 - Rev 01

**Production of Fluticasone propionate:**

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

| RESIDUAL SOLVENTS BY GC | | IHS |
|---|---|---|
| Reagents and Chemicals: | | |
| Methanol | : AR grade or equivalent | |
| Acetone | : AR grade or equivalent | |
| N-hexane | : AR grade or equivalent | |
| Methyl Ethyl Ketone | : AR grade or equivalent | |
| Tetrahydrofuran | : AR grade or equivalent | |
| Benzene | : AR grade or equivalent | |
| Triethyl amine | : AR grade or equivalent | |
| Dimethylformamide | : AR grade or equivalent | |
| Toluene | : AR grade or equivalent | |

| Standard testing procedure | Reference No. |
|---|---|
| Chromatographic Conditions: | |
| Column :<br>DB-1, 100% dimethylpolysiloxane, 30 m × 32 mm X 3.00 µm. | |
| Instrument: Make-Agilent, GC Model-7890B HS Model-7697A | |
| Name of the detector : FID (Flame-ionization detector) | |
| Carrier Gas : Nitrogen for chromatography. | |
| Injection system : Auto | |
| Instrument parameters: | |
| Initial oven temp. : 40°C | |
| Initial time : 5 minutes. | |
| Rate : 10°C/min. | |
| Final oven temp. : 240°C | |
| Final Time : 0 minutes. | |
| Injector temperature : 225°C | |
| FID temperature : 250°C | |
| Column flow ($N_2$) : 1.5 ml/min | |
| Split ratio : 2:1 | |
| Head Space Parameters: | |
| Vial oven Temperature : 80°C | |
| Loop Temperature : 90°C | |
| Transfer line temperature : 100°C | |
| Vial equilibrium : 12.00 min | |
| Inject Duration : 0.50 min | |
| Max cycle time : 37.0 min | |
| (Run + Post run + cooling + prep. run) | |
| Diluent : DMSO | |
| Injection volume : 1000 µl | |

| Standard testing procedure | Reference No. |
|---|---|
| Preparation of blank solution:<br>Transfer 5 mL of diluent to a headspace vial and seal the vial immediately. | |
| Preparation of standard stock solution:<br>Accurately weigh about 1.0 g Acetone, 0.1760 g Dimethyl Formamide, 0.1440 g of Tetrahydrofuran, 0.058 g of N-hexane, 0.60 g Methanol, 0.1780 gm of Toluene, 1.0 g of methyl ethyl ketone and 1.0 g of Triethyl amine in 100 ml volumetric flask containing about 10 ml of diluent. Make up the volume with diluent. | |
| Preparation of benzene standard stock solution:<br>Accurately weigh about 0.05 g of benzene stock solution in a 25 ml volumetric flask containing diluent about 10 ml of diluent make up the volume with diluent. Dilute 1.0 ml of this solution to 100 ml with diluent. | |
| Preparation of standard solution:<br>Dilute 10 ml of standard stock solution and 2 ml of benzene stock solution diluted to 100 ml of diluent. | Sample quantity 1.0 gm |
| Preparation of sample solution:<br>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. | |
| Evaluation of blank solution:<br>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. | |
| System suitability:<br>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 relative standard deviation of area of six replicate injections for all solvents is not more than 15.0% and resolution NLT 1.5 at every two peaks.<br>Precaution to be taken during analysis, Heat the column at 240°C for half an hour before starting the analysis. | |

| Standard testing procedure | Reference No. |
|---|---|

Injection sequence:

| Sample information | No. of injections |
|---|---|
| Diluent Blank | 01 |
| Standard solution | 06 |
| Sample solution | 01 |

Solvent elution order:

| Sr. No. | Solvents | Retention time |
|---|---|---|
| 01 | Methanol | 3.274 |
| 02. | Acetone | 4.994 |
| 03. | Methyl Ethyl Ketone | 8.043 |
| 04. | n-hexane | 8.807 |
| 05. | Tetrahydrofuran | 9.252 |
| 06. | Benzene | 10.346 |
| 07. | Triethyl amine | 11.112 |
| 08. | Dimethyl Formamide | 12.655 |
| 09. | Toluene | 13.102 |

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.

| Standard testing procedure | | Reference No. |
|---|---|---|
| Particle size: | | IHS |
| | | Sample quantity 100 mg |
| Instrument | Malvern Mastersizer 2000 Ver.5.60 | |
| Accessory | Hydro 2000S [A] | |
| Dispersant | Purified water or HPLC water | |
| Dispersant(Water) Refractive Index | 1.33 | |
| Particle(Material) Refractive Index | 1.555 | |
| Absorption | 0.1 | |
| Size Range | 0.020 µm to 2000 µm | |
| Measurement time | 10 second | |
| Background time | 10 second | |
| Analysis Model | General purpose | |
| Sensitivity | Normal | |
| Obscuration | 10% to 15% | |
| Stirrer speed | 2100 RPM | |
| Ultrasound | 50% for 1 min. | |
| Measurement per Aliquot | 3 | |
| Delay time | 2 Second | |
| 10% Tween 80 solution | 10ml of tween-80 to 100ml water (10%W/V) | |
| Sample preparation | Transfer about 100 mg sample into 100 ml beaker. Add 1.0 ml of tween 80 (10%) 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. | |

Precaution: Note that after sonication air bubbles may form at the top of the solution. Remove the bubbles by glass rod. Then perform the analysis.

Cleaning : Before and After analysis clean the HYDRO 2000S (Accessory) using LR grade Methanol 1 to 2 times