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 2020-149 - Rev 00

Name of the substance:
HALOPERIDOL

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

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 **HALOPERIDOL** no. 616 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 the following impurity by liquid chromatography (Annex 2)
  4-Chloro-1-(4-fluorophenyl) butan-1-one not more than 150 ppm

- Test for residual solvents by gas chromatography (Annex 3)
  Methanol not more than 3000 ppm

The substance is packed in two transparent polyethylene bags in two black 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.

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

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 **4 April 2023**. 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 3 pages and the third of 4 pages.
This certificate has:
lines.

On behalf of the
Director of EDQM

Strasbourg, 4 April 2023

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 2020-149 - Rev 00 for Haloperidol

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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Certification of Substances Department

Annex 1: Site(s) of production for R0-CEP 2020-149 - Rev 00

Production of Haloperidol:

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

Additional test By HPLC

Impurity -

4-chloro-1-(4-fluorophenyl) butan-1-one. : Limit : Not more than 150 PPM

Preparation of Test solution:

Dissolve 100.0 mg of the Haloperidol to be examined in methanol R and dilute to 10.0 mL with the same solvent.

Preparation of standard solution 4-chloro-1-(4-fluorophenyl)butan-1-one-150 ppm:

Dissolve 10.0 mg of 4-chloro-1-(4-fluorophenyl) butan-1-one in 100.0 ml volumetric flask containing 10 ml of methanol and diluted to up to the mark with methanol. Dilute 1.5 ml of above solution diluted to 100 ml of methanol.

Standard testing procedure

Mobile phase A: 17 g/l of tetrabutylammonium hydrogen sulphate.

Mobile phase B : Acetonitrile

Gradient programme

Time (min)	Mobile phase A (per cent V/V)	Mobile phase B (per cent V/V)
0 - 2	90	10
2 - 17	50	50
17 - 22	50	50
22-25	90	10
25-30	90	10

Chromatographic conditions:

Column: size: l = 0.1 m, Ø = 4.6 mm;

Stationary phase: base-deactivated end-capped octadecylsilyl silica gel for chromatography R (3 µm).

Flow rate: 1.5 ml/min

Detection: Spectrophotometer at 230 nm

Injection: 10 µl

Total run time: 30 min.

Relative Retention time with reference to haloperidol (retention time = about 8 min): 4-chloro-1-(4-fluorophenyl) butan-1-one = about 2.2.

Injection sequence:

Sr. No	Name of injection	No. of injection
01.	Blank	01
02.	Standard solution	03
03.	Test solution	01

Standard testing procedure

Calculation:

Calculate the content of 4-chloro-1-(4-fluorophenyl) butan-1-one (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 4-chloro-1-(4-fluorophenyl) butan-1-one from the sample solution.

r_S: Peak response of 4-chloro-1-(4-fluorophenyl) butan-1-one from theStandard solution.

C_S: Concentration of standard solution.

C_U: Concentration of sample solution.

Standard testing procedure
Residual Solvents by GC
Reagents and Chemicals:
Methanol : AR grade or equivalent
Toluene : AR grade or equivalent
Methylene dichloride : AR grade or equivalent
Benzene : AR grade or equivalent
Chromatographic Conditions
Column:
DB-624, (6% Cynopropylphenyl and 94% dimethylpolysiloxane)
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
Instrument parameters:
Initial oven temp : 50°C
Initial time : 10 minutes.
Rate : 15°C/min.
Final oven temp. : 240°C
Final Time : 2 minutes.
Injector temperature : 225°C
FID temperature : 250°C
Carrier gas (N_2) flow : 3.0 ml/min
Split ratio : 2:1

Standard testing procedure	
Head Space Parameters:	
Vial oven Temperature	: 80°C
Needle Temperature	: 90°C
Transfer line	: 100°C
Injection time	: 0.2 min
Loop fill	: 0.50 min
Pressurization time	: 0.1 min
Vial Equilibrium	: 12 min
Loop equilibrium	: 0.05 min
GC Cycle time	: 35 minutes
Diluents	: DMSO
Injection volume	: 1000 µl
Note: Purity of diluents 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.	
Preparation of blank solution:	
Transfer 5 mL of diluent to a headspace vial and seal the vial immediately.	
Preparation of standard stock solution:	
Accurately weigh about 0.60 g Methanol, 0.1780 g Toluene and 0.12 g of methylene dichloride in 100 ml volumetric flask containing about 10 ml of diluent. Make up the volume with diluent.	
Preparation of Benzene standard stock solution:	
Accurately weigh about 0.05 g of Benzene in a 25 ml volumetric flask containing about 10 ml of diluent, make up the volume with diluent. Dilute 1.0 ml of this solution to 100 ml with diluent	

Standard testing procedure

Preparation of standard solution:

Dilute 10 ml of standard stock solution and 2.0 ml of Benzene stock solution in 100 ml of volumetric flask containing about 10.0 ml of diluent and dilute up to the mark with diluent.

Preparation of sample solution:

Accurately weigh and transfer about 1.0 g of sample to the headspace vial ar add 5.0 ml of diluent & seal the vial immediately.

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.

Sr. No.	Name of solvent	RT (About)
01.	Methanol	3.6
02.	Methylene dichloride	6.12
03.	Benzene	10.0
04.	Toluene	15.0

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 relative standard deviation of area of six replicate injections for all solvents is not more than 15.0% and Retention time NMT 2.0%, Resolution should be not less than 1.5.

Precaution to be taken during analysis. Heat the column at 240°C for half an hour before starting the analysis.

Standard testing procedure:

Injection sequence:

Sr. No.	Name of Injection	No. of injections
01.	Diluent Blank	01
02.	Standard solution	06
03.	Sample solution	01

Calculation:

Calculate 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.