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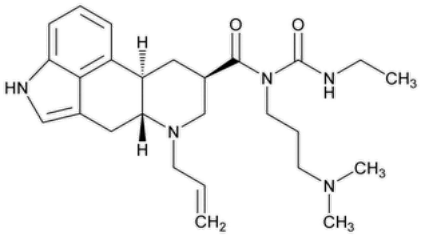
Cabergoline



$C_{26}H_{37}N_5O_2$ 451.60

Ergoline-8β-carboxamide, *N*-[3-(dimethylamino)propyl]-*N*-[(ethylamino)carbonyl]-6-(2-propenyl)-;
1-[(6-Allylergolin-8β-yl)carbonyl]-1-[3-(dimethylamino)propyl]-3-ethylurea CAS RN®: 81409-90-7; UNII: LL60K9J05T.

DEFINITION

Cabergoline contains NLT 98.0% and NMT 102.0% of cabergoline ($C_{26}H_{37}N_5O_2$), calculated on the anhydrous basis for the crystalline form and on the anhydrous and solvent-free basis for the amorphous form.

IDENTIFICATION

• **A.** **Spectroscopic Identification Tests ⟨197⟩, *Infrared Spectroscopy*: 197K**

Change to read:

• **B.**

Proceed as directed for *Procedure 1* or *Procedure 2*. The criteria for *Procedure 1* or *Procedure 2* must be met.

Procedure 1: *Crystallinity ⟨695⟩*

Acceptance criteria

For the crystalline form: Meets the requirements

For the amorphous form: Does not meet the requirements

Procedure 2: ▲*X-Ray Powder Diffraction ⟨941⟩*▲ (CN 1-May-2022)

Acceptance criteria

For the crystalline form: A diffraction pattern is present.

For the amorphous form: No diffraction pattern is present.

• **C.** The retention time of the major peak of the *Sample solution* corresponds to that of the *Standard solution*, as obtained in the *Assay*.

ASSAY

• **Procedure**

Prepare solutions immediately before use, and protect from light.

Buffer: Dissolve 6.8 g of monobasic potassium phosphate in 900 mL of water, adjust with phosphoric acid to a pH of 2.0, and dilute to 1 L. Add 0.2 mL of triethylamine to the resulting solution and mix.

Mobile phase: Acetonitrile and *Buffer* (4:21)

Standard solution: 0.25 mg/mL of USP Cabergoline RS in *Mobile phase*. Sonicate if needed.

Sample solution: 0.25 mg/mL of Cabergoline in *Mobile phase*. Sonicate if needed.

Chromatographic system

(See *Chromatography ⟨621⟩, System Suitability*.)

Mode: LC

Detector: UV 280 nm

Column: 4.0-mm × 25-cm; 10-µm packing L1

Flow rate: 1.3 mL/min

Injection volume: 100 µL

System suitability

Sample: *Standard solution*

Suitability requirements

Column efficiency: NLT 1000 theoretical plates

Relative standard deviation: NMT 2.0% for five replicate injections

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of cabergoline ($C_{26}H_{37}N_5O_2$) in the portion of Cabergoline taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times 100$$

r_U = peak response from the *Sample solution*

r_S = peak response from the *Standard solution*

C_S = concentration of USP Cabergoline RS in the *Standard solution* (mg/mL)

C_U = concentration of Cabergoline in the *Sample solution* (mg/mL)

Acceptance criteria

For the crystalline form: 98.0%–102.0% on the anhydrous basis

For the amorphous form: 98.0%–102.0% on the anhydrous and solvent-free basis

IMPURITIES

• **Residue on Ignition ⟨281⟩:** NMT 0.1%

• **Organic Impurities**

Prepare solutions immediately before use, and protect from light.

Buffer and **Mobile phase:** Proceed as directed in the *Assay*.

System suitability solution: To 10 mL of 0.1 M sodium hydroxide add 50 mg of Cabergoline and stir for about 15 min. To 1 mL of the suspension add 1 mL of 0.1 M hydrochloric acid, and dilute with *Mobile phase* to 10.0 mL. Sonicate until dissolution is complete. [Note—The main degradation product obtained is cabergoline related compound A.]

Sample solution: 0.25 mg/mL of Cabergoline in *Mobile phase*. Sonicate if needed.

Chromatographic system

(See *Chromatography ⟨621⟩, System Suitability*.)

Mode: LC

Detector: UV 280 nm

Column: 4.0-mm × 25-cm; 10-µm packing L1

Flow rate: 1.3 mL/min

Injection volume: 100 µL

System suitability

Sample: *System suitability solution*

[Note—See *Table 1* for relative retention times.]

Suitability requirements

Resolution: NLT 3.0 between cabergoline and cabergoline related compound A

Analysis

Sample: *Sample solution*

Calculate the percentage of each impurity in the portion of Cabergoline taken:

$$\text{Result} = (r_U/r_T) \times 100$$

r_U = peak response of each impurity from the *Sample solution*

r_T = sum of all the peak responses from the *Sample solution*

Acceptance criteria: See *Table 1*.

Table 1

Name	Relative Retention Time	Acceptance Criteria, NMT (%)
Cabergoline related compound D[a]	0.3	0.1
Cabergoline related compound B[b]	0.6	0.1
Cabergoline related compound A[c]	0.8	0.3
Cabergoline	1.0	—

Name	Relative Retention Time	Acceptance Criteria, NMT (%)
Cabergoline related compound C[d]	2.9	0.3
Any other individual unidentified impurity	—	0.10
Total impurities	—	0.8

[a] (6a*R*,9*R*,10a*R*)-*N*-[3-(Dimethylamino)propyl]-7-(prop-2-enyl)-4,6,6a,7,8,9,10,10a-octahydroindolo[4,3-*fg*]quinoline-9-carboxamide.

[b] (6a*R*,9*R*,10a*R*)-N^9-[3-(Dimethylamino)propyl]-N^4-ethyl-7-(prop-2-enyl)6a,7,8,9,10,10a-hexahydroindolo[4,3-*fg*]quinoline-4,9(6*H*)-dicarboxamide.

[c] (6a*R*,9*R*,10a*R*)-7-(Prop-2-enyl)-4,6,6a,7,8,9,10,10a-octahydroindolo[4,3-*fg*]quinoline-9-carboxylic acid.

[d] (6a*R*,9*R*,10a*R*)-N^9-[3-(Dimethylamino)propyl]-N^4-ethyl-N^9-(ethylcarbamoyl)-7-(prop-2-enyl)-6a,7,8,9,10,10a-hexahydroindolo[4,3-*fg*]quinoline-4,9(6*H*)-dicarboxamide.

SPECIFIC TESTS

• **Optical Rotation,** *Specific Rotation* ⟨781S⟩

Sample solution: 1 mg/mL in alcohol

Acceptance criteria

For the crystalline form: −77° to −83° on the anhydrous basis

For the amorphous form: −77° to −83° on the anhydrous and solvent-free basis

• **Water Determination,** *Method I* ⟨921⟩

Acceptance criteria

For the crystalline form: NMT 0.5%

For the amorphous form: NMT 1.5%

ADDITIONAL REQUIREMENTS

• **Packaging and Storage:** Preserve in tight containers, protected from light. If it is labeled as amorphous, preserve under nitrogen in tight containers, store cold, and protect from light.

• **Labeling:** Where it is the amorphous form, the label so indicates.

• **USP Reference Standards** ⟨11⟩

USP Cabergoline RS

Auxiliary Information - Please check for your question in the FAQs before contacting USP.

Topic/Question	Contact	Expert Committee
CABERGOLINE	Documentary Standards Support	SM42020 Small Molecules 4

Chromatographic Database Information: Chromatographic Database

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