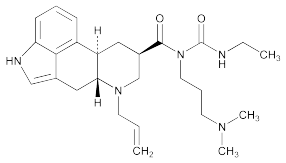
Cabergoline



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

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

DEFINITION

Cabergoline contains NLT 98.0% and NMT 102.0% of the labeled amount of $C_{26}H_{37}N_5O_2$, calculated on the anhydrous basis.

IDENTIFICATION

- **A. INFRARED ABSORPTION ⟨197K⟩**
- **B.** 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**

[NOTE—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*. [NOTE—Sonicate if needed.]

Sample solution: 0.25 mg/mL of Cabergoline in *Mobile phase*. [NOTE—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 size: 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 $C_{26}H_{37}N_5O_2$ in the portion of Cabergoline taken:

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

r_U = peak response of the *Sample solution*

r_S = peak response of 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: 98.0%–102.0% on the anhydrous basis

IMPURITIES

Inorganic Impurities

- **RESIDUE ON IGNITION ⟨281⟩:** NMT 0.1%
- **HEAVY METALS,** *Method II* ⟨**231**⟩**:** 20 ppm

Organic Impurities

- **PROCEDURE**

[NOTE—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*. [NOTE—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 size: 100 µL

System suitability

Sample: *System suitability solution*

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 the peak responses for all peaks from the *Sample solution*

Acceptance criteria

Individual impurities: See *Impurity Table 1*.

Total impurities: NMT 0.8%

Impurity 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	—

[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-(prop2-enyl)-6a,7,8,9,10,10a-hexahydroindolo[4,3-*fg*]quinoline-4,9(6*H*)-dicarboxamide.

Impurity Table 1 *(Continued)*

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

[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-(prop2-enyl)-6a,7,8,9,10,10a-hexahydroindolo[4,3-*fg*]quinoline-4,9(6*H*)-dicarboxamide.

SPECIFIC TESTS

- **Optical Rotation,** *Specific Rotation* ⟨**781S**⟩**:** −77° to −83°
  Sample solution: 1 mg/mL in alcohol, on the anhydrous basis
- **Water Determination,** *Method I* ⟨**921**⟩**:** NMT 0.5%

ADDITIONAL REQUIREMENTS

- **Packaging and Storage:** Preserve in tight containers, protected from light.
- **USP Reference Standards** ⟨**11**⟩
  USP Cabergoline RS

Cabergoline Tablets

» Cabergoline Tablets contain not less than 90.0 percent and not more than 110.0 per cent of the labeled amount of cabergoline ($C_{26}H_{37}N_5O_2$).

Packaging and storage—Preserve in light-resistant, tight containers, and store at controlled room temperature.

USP Reference standards ⟨11⟩**—**
USP Cabergoline RS

Identification—The retention time of the major peak in the chromatogram of the *Assay preparation* corresponds to that in the chromatogram of the *Standard preparation,* as obtained in the *Assay.*

Dissolution ⟨711⟩**—**

Medium: 0.1 N hydrochloric acid; 500 mL, degassed with helium.

Apparatus 2: 50 rpm.

Time: 15 minutes.

Determine the amount of $C_{26}H_{37}N_5O_2$ dissolved by employing the following procedure.

Mobile phase and *Chromatographic system*—Prepare as directed in the *Assay.*

Standard solution—Dissolve an accurately weighed quantity of USP Cabergoline RS in *Medium* to obtain a solution having a known concentration of about 1 µg per mL.

Test solution—Pass the solution under test through a suitable filter, discarding the first few mL.

Chromatographic system (see *Chromatography* ⟨621⟩)—Prepare as directed in the *Assay*. Chromatograph the *Standard solution,* and record the peak responses as directed for *Procedure:* the column efficiency is not less than 3000 theoretical plates; and the relative standard deviation for replicate injections is not more than 2%.

Procedure—Separately inject equal volumes (about 100 µL) of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure the peak responses. Calculate the percentage of $C_{26}H_{37}N_5O_2$ dissolved by the formula:

$$\frac{r_U \times C_S \times 500 \times 100}{r_S \times L}$$

in which r_U and r_S are the responses for the cabergoline peak obtained from the *Test solution* and the *Standard solution,* respectively; C_S is the concentration of USP Cabergoline RS, in mg per mL, in the *Standard solution;* 500 is the volume of *Medium;* and L is the Tablet label claim, in mg per Tablet.

Tolerances—Not less than 75% (Q) of the labeled amount of $C_{26}H_{37}N_5O_2$ is dissolved in 15 minutes.

Uniformity of dosage units ⟨905⟩**:** meet the requirements.

Chromatographic purity—[NOTE—Prepare solutions immediately before use, and protect from light.]

Mobile phase—Prepare as directed in the *Assay*.

Resolution solution—To 10 mL of 0.1 M sodium hydroxide add 50 mg of cabergoline. Stir for about 15 minutes. To 1 mL of the suspension add 1 mL of 0.1 M hydrochloric acid, and dilute with *Mobile phase* to 10 mL. Sonicate until dissolution is complete. The main degradation product obtained is cabergoline related compound A.

Test solution—Use the *Assay preparation,* prepared as directed in the *Assay.*

Chromatographic system (see *Chromatography* ⟨621⟩)—Prepare as directed in the *Assay*. Chromatograph (about 20 µL) of the *Resolution solution,* and record the peak responses as directed for *Procedure.* Identify the peaks due to cabergoline related compound A and cabergoline using the relative retention times (RRT) given in *Table 1:* the resolution, *R,* between cabergoline and cabergoline related compound A is not less than 3.0.

Procedure—Inject a volume (about 100 µL) of the *Test solution* into the chromatograph, and record the chromatogram. Calculate the percentage of each impurity in the portion of Tablets taken by the formula:

$$100(r_i / r_s)$$

in which r_i is the peak area of each impurity obtained from the *Test solution;* and r_s is the sum of the peak areas of all the impurities and the main peak due to cabergoline obtained from the *Test solution.* Calculate the percentage of total impurities in the portion of Tablets taken by the formula:

$$100(r_t / r_s)$$

in which r_t is the sum of the peak areas of all the impurities obtained from the *Test solution;* and r_s is the sum of the peak areas of all the impurities and the main peak due to cabergoline obtained from the *Test solution.* The relative retention times and limits for cabergoline related compounds A and cabergoline *N*-oxide are given in *Table 1*.

Table 1

Name	RRT	Limit (%)
Cabergoline related compound A[1]	0.8	NMT 2.0
Cabergoline	1.0	—
Cabergoline *N*-oxide[2]	1.4	NMT 1.0
Any unspecified degradation product	—	NMT 0.5
Total	—	NMT 2.5

[1] (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.
[2] (6a*R*,9*R*,10a*R*)-7-Allyl-*N*-(3-(dimethylazinoyl)propyl)-*N*-(ethylcarbamoyl)-4,6,6a,7,8,9,10,10a-octahydroindolo[4,3-*fg*]quinoline-9-carboxamide.