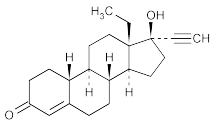
Levonorgestrel



$C_{21}H_{28}O_2$ 312.45
18,19-Dinorpregn-4-en-20-yn-3-one, 13-ethyl-17-hydroxy-, (17α)-(–)-.
(–)-13-Ethyl-17-hydroxy-18,19-dinor-17α-pregn-4-en-20-yn-3-one [797-63-7].

» Levonorgestrel contains not less than 98.0 percent and not more than 102.0 percent of $C_{21}H_{28}O_2$, calculated on the dried basis.

Packaging and storage—Preserve in well-closed, light-resistant containers.

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

Identification—

A: *Infrared Absorption* ⟨197K⟩.

B: Meeting the requirements of the tests for *Specific rotation* and *Melting range* provides identification distinguishing it from norgestrel.

Melting range ⟨741⟩: between 232° and 239°, but the range between beginning and end of melting does not exceed 4°.

Specific rotation ⟨781S⟩: between –30° and –35°.

Test solution: 20 mg per mL, in chloroform.

Loss on drying ⟨731⟩**—**Dry it at 105° for 5 hours: it loses not more than 0.5% of its weight.

Residue on ignition ⟨281⟩: not more than 0.3%.

Limit of ethynyl group—Dissolve 200 mg in about 40 mL of tetrahydrofuran. Add 10 mL of silver nitrate solution (1 in 10), and titrate with 0.1 N sodium hydroxide VS, using either a glass-calomel or a silver-silver chloride electrode system with potassium nitrate filling solution. Perform a blank determination, and make any necessary correction. Each mL of 0.1 N sodium hydroxide is equivalent to 2.503 mg of ethynyl group (-C≡CH). Not less than 7.81% and not more than 8.18% of ethynyl group is found.

Chromatographic purity—Proceed as directed in the test for *Chromatographic purity* under *Norgestrel,* using USP Levonorgestrel RS in place of USP Norgestrel RS. The requirements of the test are met if the sum of the impurities in the *Test preparation* does not exceed 2.0% and no single impurity is greater than 0.5%.

Assay—Using USP Levonorgestrel RS, proceed as directed in the *Assay* under *Norgestrel*, except to read "Levonorgestrel" in place of "Norgestrel."

Levonorgestrel and Ethinyl Estradiol Tablets

DEFINITION

Levonorgestrel and Ethinyl Estradiol Tablets contain NLT 90.0% and NMT 110.0% of the labeled amount of levonorgestrel ($C_{21}H_{28}O_2$) and NLT 90.0% and NMT 110.0% of the labeled amount of ethinyl estradiol ($C_{20}H_{24}O_2$).

IDENTIFICATION

• **A.** The retention times of the two major peaks of the *Sample solution* correspond to those of levonorgestrel and ethinyl estradiol in the *Standard solution*, as obtained in the *Assay*.

• **B.** Finely powder 20 Tablets and transfer a portion of the powder, equivalent to 4 mg of levonorgestrel, to a suitable container. Add 250 mL of a solvent mixture consisting of isooctane and chloroform (3:1). Sonicate the mixture for 3 min, and then stir it by mechanical means for 30 min. Filter the mixture and evaporate the filtrate to dryness in a rotating vacuum evaporator. Dissolve the residue in 3 mL of chloroform, and transfer with a pipet to a 60-mL separator containing 18 mL of isooctane. Rinse the evaporator flask with an additional 3-mL portion of chloroform, and add the rinsing to the separator. Add 10 mL of 1 N sodium hydroxide, shake vigorously, and allow the layers to separate. Discard the lower aqueous phase, and filter the organic phase through 3 g of anhydrous sodium sulfate on filter paper into a 50-mL beaker. Rinse the filter with several small portions of the mixture of isooctane and chloroform (3:1), adding the filtered rinsings to the filtrate, and evaporate under nitrogen on a steam bath to dryness. Dissolve the residue in 1–2 mL of hot toluene, and transfer with a pipet to a small glass vial. Reduce the volume of the solution to 0.1 mL under nitrogen with warming. [NOTE—During this step, any crystals that deposit on the vial wall should be transferred to the bottom, and allowed to redissolve.]

Store the vial containing the clear toluene solution at 4° overnight to allow crystallization to occur. Remove and discard the mother liquor with a pipet, rinse the crystals with two 0.5-mL portions of anhydrous ether, and discard the rinsings. Dry the vial containing the rinsed crystals in a vacuum desiccator at 60° for 4 h.

Acceptance criteria: The melting point of the dried crystals of levonorgestrel so obtained is not lower than 220°, using the procedure described under *Melting Range or Temperature* ⟨741⟩*, Class I*.

ASSAY

• **PROCEDURE**

Mobile phase: Acetonitrile, methanol, and water (35:15:45)

Standard solution: 15 µg/mL of USP Levonorgestrel RS and 3 µg/mL of USP Ethinyl Estradiol RS in *Mobile phase*

Sample solution: Transfer a number of Tablets, equivalent to 3 mg of levonorgestrel, to a 200-mL volumetric flask. Dilute with *Mobile phase* to volume, sonicate to disintegrate the Tablets, then shake by mechanical means for 20 min. Centrifuge, and use the clear supernatant.

Chromatographic system
(See *Chromatography* ⟨621⟩*, System Suitability*.)
Mode: LC
Detector: UV 215 nm
Column: 4.6-mm × 15-cm; 5- to 7-µm packing L7
Flow rate: 1 mL/min
Injection size: 50 µL

System suitability
Sample: *Standard solution*
[NOTE—The relative retention times for ethinyl estradiol and levonorgestrel are about 0.7 and 1.0, respectively.]
Suitability requirements
Resolution: NLT 2.5 between the two major peaks
Relative standard deviation: NMT 2.0%

Analysis
Samples: *Standard solution* and *Sample solution*
Calculate the percentage of $C_{21}H_{28}O_2$ and $C_{20}H_{24}O_2$ in the portion of Tablets taken:

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

r_U = peak response of the corresponding analyte from the *Sample solution*
r_S = peak response of the corresponding analyte from the *Standard solution*
C_S = concentration of the appropriate USP Reference Standard in the *Standard solution* (µg/mL)
C_U = nominal concentration of the corresponding analyte in the *Sample solution* (µg/mL)

Acceptance criteria: 90.0%–110.0% of the labeled amount of $C_{21}H_{28}O_2$, 90.0%–110.0% of the labeled amount of $C_{20}H_{24}O_2$

PERFORMANCE TESTS

• **DISSOLUTION ⟨711⟩:** Determine the amount of $C_{21}H_{28}O_2$ and $C_{20}H_{24}O_2$ dissolved by employing the following method.
Medium: Polysorbate 80 (5 µg/g) in water; 500 mL
Apparatus 2: 75 rpm
Time: 60 min
Mobile phase: Acetonitrile and water (6:4)
Standard solution: Prepare a solution of USP Levonorgestrel RS and USP Ethinyl Estradiol RS in *Medium* having known concentrations corresponding approximately to the concentrations that would be obtained by dissolving 1 Tablet in 500 mL of *Medium*.
[NOTE—A volume of alcohol not exceeding 2% of the final total volume of solution may be used to aid in dissolving the Reference Standards.]
Sample solution: Withdraw 15-mL portions of liquid from each vessel, and pass through a polyvinylidene filter, discarding the first 10 mL of the filtrate.
Chromatographic system
(See *Chromatography* ⟨621⟩*, System Suitability*.)
Mode: LC
Detector: UV 247 nm (for levonorgestrel analysis); a spectrofluorometric detector (for ethinyl estradiol analysis), with an excitation wavelength of 285 nm, and an emission wavelength of 310 nm
Column: 4-mm × 15-cm; packing L7
Flow rate: 1 mL/min
Injection size: 100 µL
System suitability
Sample: *Standard solution*
[NOTE—The relative retention times for ethinyl estradiol and levonorgestrel are about 0.7 and 1.0, respectively.]
Suitability requirements
Relative standard deviation: NMT 3.0%
Analysis
Samples: *Standard solution* and *Sample solution*
Calculate the percentage of $C_{21}H_{28}O_2$ and $C_{20}H_{24}O_2$ dissolved:

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

r_U = peak response of the corresponding analyte from the *Sample solution*
r_S = peak response of the corresponding analyte from the *Standard solution*
C_S = concentration of the appropriate USP Reference Standard in the *Standard solution* (µg/mL)
C_U = nominal concentration of the corresponding analyte in the *Sample solution* (µg/mL)

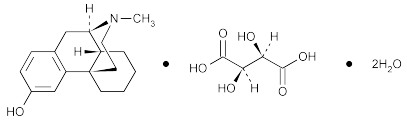
Tolerances
Uncoated Tablets: NLT 80% (Q) of the labeled amount of $C_{21}H_{28}O_2$, and 75% (Q) of the labeled amount of $C_{20}H_{24}O_2$ is dissolved.
Coated Tablets: NLT 60% (Q) of the labeled amount of $C_{21}H_{28}O_2$ and $C_{20}H_{24}O_2$ is dissolved.

• **UNIFORMITY OF DOSAGE UNITS ⟨905⟩:** Meet the requirements
Sample solution: Place 1 Tablet in a 40-mL centrifuge tube, add 10.0 mL of *Mobile phase*, and proceed as directed in the *Assay*.

ADDITIONAL REQUIREMENTS

• **PACKAGING AND STORAGE:** Preserve in well-closed containers.
• **USP REFERENCE STANDARDS ⟨11⟩**
USP Ethinyl Estradiol RS
USP Levonorgestrel RS

Levorphanol Tartrate



$C_{17}H_{23}NO \cdot C_4H_6O_6 \cdot 2H_2O$ 443.49
Morphinan-3-ol, 17-methyl-, [*R*-(*R**,*R**)]-2,3-dihydroxybutanedioate (1:1) (salt), dihydrate.
17-Methylmorphinan-3-ol, tartrate (1:1) (salt) dihydrate [5985-38-6].
Anhydrous 407.47 [125-72-4].

» Levorphanol Tartrate contains not less than 99.0 percent and not more than 101.0 percent of $C_{17}H_{23}NO \cdot C_4H_6O_6$, calculated on the anhydrous basis.

Packaging and storage—Preserve in well-closed containers. Store at 25°, excursions permitted between 15° and 30°.

USP Reference standards ⟨11⟩—
USP Levorphanol Tartrate RS

Identification—

A: *Infrared Absorption* ⟨197K⟩—Obtain the test specimen as follows. Dissolve 50 mg in 25 mL of water in a 125-mL separator. Add 2 mL of 6 N ammonium hydroxide, extract with 25 mL of chloroform, and filter the chloroform extract through a layer of 4 g of granular anhydrous sodium sulfate supported on glass wool into a 125-mL conical flask. Evaporate the chloroform extract on a steam bath with the aid of a stream of nitrogen to dryness. Dissolve the residue in 1 mL of acetone, and evaporate to dryness. Dry in vacuum at 90° for 1 hour. Proceed as directed with the dried levorphanol so obtained and a similar preparation of USP Levorphanol Tartrate RS.

B: *Ultraviolet Absorption* ⟨197U⟩—

Solution: 130 µg per mL.

Medium: 0.1 N hydrochloric acid.

Absorptivities at 279 nm, calculated on the anhydrous basis, do not differ by more than 3.0%.

Specific rotation ⟨781S⟩: between –14.7° and –16.3°.

Test solution: 30 mg per mL, in water. Heat on a water bath or sonicate to dissolve 750 mg in 20 mL of water in a 25-mL volumetric flask, dilute with water to volume, and mix.

Water, *Method I* ⟨921⟩**:** between 7.0% and 9.0%.

Residue on ignition ⟨281⟩: not more than 0.1%.

Ordinary impurities ⟨466⟩—

Test solution: water.

Standard solution: water.

Eluant: a mixture of hexanes, dehydrated alcohol, and ammonium hydroxide (80:25:1).

Visualization: 17; then view immediately under short-wavelength UV light.

Assay—Dissolve about 900 mg of sample, accurately weighed, in 85 mL of glacial acetic acid, warming slightly if necessary. Titrate with 0.1 N perchloric acid VS and determine the endpoint potentiometrically. Perform a blank determination and make any nececssary corrections. Each mL of 0.1 N perchloric acid consumed by the sample is equivalent to 40.75 mg of $C_{17}H_{23}NO \cdot C_4H_6O_6$.