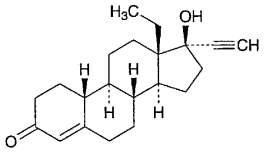
Norgestrel

ノルゲストレル



$C_{21}H_{28}O_2$: 312.45
13-Ethyl-17-hydroxy-18,19-dinor-17α-pregn-4-en-20-yn-3-one [*6533-00-2*]

Norgestrel, when dried, contains not less than 98.0% of $C_{21}H_{28}O_2$.

Description Norgestrel occurs as white crystals or crystalline powder.

It is soluble in tetrahydrofuran and in chloroform, sparingly soluble in ethanol (95), slightly soluble in diethyl ether, and practically insoluble in water.

Identification (1) Dissolve 1 mg of Norgestrel in 2 mL of ethanol (95), and add 1 mL of sulfuric acid: a red-purple color develops. With this solution, examine under ultraviolet light (main wavelength: 365 nm): the solution shows a red-orange fluorescence.

(2) Determine the infrared absorption spectrum of Norgestrel, previously dried, as directed in the potassium bromide disk method under the Infrared Spectrophotometry, and compare the spectrum with the Reference Spectrum: both spectra exhibit similar intensities of absorption at the same wave numbers.

Melting point 206 - 212°C

Purity (1) Heavy metals—Take 1.0 g of Norgestrel, heat gently to carbonize, cool, add 10 mL of a solution of magnesium nitrate hexahydrate in ethanol (95) (1 in 10), and ignite the ethanol to burn. After cooling, add 1 mL of sulfuric acid, proceed with this solution according to Method 4, and perform the test. Prepare the control solution with 2.0 mL of Standard Lead Solution (not more than 20 ppm).

(2) Other steroids—Dissolve 0.030 g of Norgestrel in 5 mL of chloroform, and use this solution as the sample solution. Pipet 1 mL of the sample solution, add chloroform to make exactly 100 mL, and use this solution as the standard solution. Perform the test with these solutions as directed under the Thin-layer Chromatography. Spot 10 μL each of the sample solution and the standard solution on a plate of silica gel with fluorescent indicator for thin-layer chromatography. Develop the plate with a mixture of dichloromethane and ethyl acetate (2:1) to a distance of about 10 cm, and air-dry the plate. Examine under ultraviolet light (main wavelength: 254 nm): the spots other than the principal spot from the sample solution are not more intense than the spot from the standard solution.

Loss on drying Not more than 0.5% (1 g, 105°C, 3 hours).

Residue on ignition Not more than 0.2% (0.5 g).

Assay Weigh accurately about 0.2 g of Norgestrel, previously dried, dissolve in 40 mL of tetrahydrofuran, add 10 mL of a solution of silver nitrate (1 in 20), and titrate with 0.1 mol/L sodium hydroxide VS (potentiometric titration). Perform a blank determination, and make any necessary correction.

Each mL of 0.1 mol/L sodium hydroxide VS
= 31.245 mg of $C_{21}H_{28}O_2$

Containers and storage Containers—Well-closed containers.

Norgestrel and Ethinylestradiol Tablets

ノルゲストレル・エチニルエストラジオール錠

Norgestrel and Ethinylestradiol Tablets contain not less than 90% and not more than 110% of the labeled amount of norgestrel ($C_{21}H_{28}O_2$: 312.45) and ethinylestradiol ($C_{20}H_{24}O_2$: 296.40).

Method of preparation Prepare as directed under the Tablets, with Norgestrel and Ethinylestradiol.

Identification (1) Weigh a quantity of Norgestrel and Ethinylestradiol Tablets, equivalent to 10 mg of Norgestrel according to the labeled amount, previously powdered, add 10 mL of chloroform, shake for 10 minutes, and filter. To 2 mL of the filtrate add 6 mL of sodium hydroxide TS, shake vigorously, and centrifuge. Take 1 mL of the chloroform layer, evaporate on a water bath to dryness, dissolve the residue in 2 mL of ethanol (95), and add 1 mL of sulfuric acid: a red-purple color develops. Examine under ultraviolet light (main wavelength: 365 nm): this solution shows a red-orange fluorescence (norgestrel).

(2) Take 1 mL of the filtrate obtained in (1), evaporate on a water bath to dryness, add 1 mL of boric acid-methanol buffer solution to the residue, shake, and cool in ice. Add 1 mL of ice-cold diazo TS, shake, add 1 mL of sodium hydroxide TS, and shake: a red-orange color develops (ethinylestradiol).

(3) Use the filtrate obtained in (1) as the sample solution. Separately, dissolve 10 mg of Norgestrel Reference Standard and 1 mg of Ethinylestradiol Reference Standard, respectively, in 10 mL of chloroform, and use these solutions as the standard solution (1) and the standard solution (2). Perform the test with these solutions as directed under the Thin-layer Chromatography. Spot 20 μL each of the sample solution and the standard solutions (1) and (2) on a plate of silica gel for thin-layer chromatography. Develop the plate with a mixture of 1,2-dichloroethane, methanol and water (368:32:1) to a distance of about 10 cm, and air-dry the plate. Spray evenly a solution of *p*-toluenesulfonate in ethanol (95) (1 in 5) on the plate, and heat at 105°C for 5 minutes. Examine under ultraviolet light (main wavelength: 365nm): two spots from the sample solution show the similar color tone and *Rf* value to each spot from the standard solution (1) and (2).

Content uniformity Add 2 mL of diluted methanol (7 in 10) to 1 tablet of Norgestrel and Ethinylestradiol Tablets, add exactly 2 mL of the internal standard solution, shake for 20 minutes, and centrifuge. Filter the supernatant liquid

through a membrane filter with pore size of not more than 0.2 μm, and use this filtrate as the sample solution. Separately, weigh accurately quantities of Norgestrel Reference Standard, previously dried at 105°C for 3 hours, and of Ethinylestradiol Reference Standard, previously dried in a desiccator (in vacuum, phosphorus (V) oxide) for 4 hours, equivalent to 100 times each of the labeled amounts, dissolve in diluted methanol (7 in 10) to make exactly 200 mL. Pipet 2 mL each of the solutions, add exactly 2 mL of the internal standard solution, and use these solutions as the standard solution. Perform the test with 20 μL each of the sample solution and the standard solution as directed under the Liquid Chromatography according to the operating conditions in the Assay. Calculate the ratios, Q_{Ta} and Q_{Tb}, of the peak areas of norgestrel and ethinylestradiol to the peak area of the internal standard of the sample solution and also the ratios, Q_{Sa} and Q_{Bb}, of the peak areas of norgestrel and ethinylestradiol to the peak area of the internal standard of the standard solution.

Amount (mg) of norgestrel ($C_{21}H_{28}O_2$)
= amount (mg) of Norgestrel Reference Standard
$\times \frac{Q_{Ta}}{Q_{Sa}} \times \frac{1}{100}$

Amount (mg) of ethinylestradiol ($C_{20}H_{24}O_2$)
= amount (mg) of Ethinylestradiol Reference Standard
$\times \frac{Q_{Tb}}{Q_{Sb}} \times \frac{1}{100}$

Internal standard solution—A solution of diphenyl in diluted methanol (7 in 10) (1 in 50,000).

Dissolution test Perform the test with 1 tablet of Norgestrel and Ethinylestradiol Tablets at 50 revolutions per minute according to Method 2 under the Dissolution Test, using 900 mL of water as the test solution. Take 50 mL or more of the dissolved solution 45 minutes after starting the test, and membrane filter through a membrane filter with pore size of not more than 0.8 μm. Discard the first 10 mL of the filtrate, transfer exactly 30 mL of the subsequent into a chromatography column [prepared by packing 0.36 g of octadecylsilanized silica gel for pretreatment (55 to 105 μm in particle diameter) in a tube about 1 cm in inside diameter]. After washing the column with 15 mL of water, elute with 3 mL of methanol, and evaporate the effluent on a water bath to dryness at about 40°C with the aid of a current air. Dissolve the residue in exactly 2 mL of diluted methanol (7 in 10), and use this solution as the sample solution. Separately, weigh accurately about 0.025 mg of Norgestrel Reference Standard previously dried at 105°C for 3 hours and about 2.5 mg of Ethinylestradiol Reference Standard previously dried in a desiccator (in vacuum, phosphorus (V) oxide) for 4 hours, dissolve in diluted methanol (7 in 10) to make exactly 100 mL, then pipet 3 mL of this solution, add diluted methanol (7 in 10) to make exactly 100 mL, and use this solution as the standard solution. Perform the test with 50 μL each of the sample solution and the standard solution as directed under the Liquid Chromatography according to the operating conditions as directed in the Assay. Determine the peak areas, A_{Ta} and A_{Tb}, of norgestrel and ethinylestradiol from the sample solution, and the peak areas, A_{Sa} and A_{Sb}, of norgestrel and ethinylestradiol from the standard solution.

The dissolution rate of Norgestrel and Ethinylestradiol Tablets in 45 minutes is not less than 70%.

Dissolution rate (%) with respect to the labeled amount of norgestrel ($C_{21}H_{28}O_2$)
$= W_{Sa} \times \frac{A_{Ta}}{A_{Sa}} \times \frac{1}{C_a} \times 1.8$

Dissolution rate (%) with respect to the labeled amount of ethinylestradiol ($C_{20}H_{24}O_2$)
$= W_{Sb} \times \frac{A_{Tb}}{A_{Sb}} \times \frac{1}{C_b} \times 1.8$

W_{Sa}: Amount (mg) of Norgestrel Reference Standard.
W_{Sb}: Amount (mg) of Ethinylestradiol Reference Standard.
C_a: Labeled amount (mg) of norgestrel ($C_{21}H_{28}O_2$) in 1 tablet.
C_b: Labeled amount (mg) of ethinylestradiol ($C_{20}H_{24}O_2$) in 1 tablet.

Assay Weigh accurately not less than 20 Norgestrel and Ethinylestradiol Tablets, and powder. Weigh accurately a portion of the powder, equivalent to about 1 mg of norgestrel ($C_{21}H_{28}O_2$), add 4 mL of diluted methanol (7 in 10), add exactly 4 mL of the internal standard solution, shake for 20 minutes, and centrifuge. Filter the supernatant liquid through a membrane filter with pore size of not more than 0.2 μm, and use this filtrate as the sample solution. Separately,weigh accurately about 0.05 g of Norgestrel Reference Standard, previously dried at 105°C for 3 hours, and about 5 mg of Ethinylestradiol Reference Standard, previously dried in a desiccator (in vacuum, phosphorus (V) oxide) for 4 hours, dissolve in diluted methanol (7 in 10) to make exactly 200 mL, respectively. Pipet 4 mL each of the solutions, add exactly 4 mL of the internal standard solution, and use these solutions as the standard solution. Perform the test with 20 μL each of the sample solution and the standard solution as directed under the Liquid Chromatography according to the following conditions. Calculate the ratios, Q_{Ta} and Q_{Tb}, of the peak areas of norgestrel and ethinylestradiol to the peak area of the internal standard of the sample solution and also the ratios, Q_{Sa} and Q_{Sb}, of the peak areas of norgestrel and ethinylestradiol to the peak area of the internal standard of the standard solution.

Amount (mg) of norgestrel ($C_{21}H_{28}O_2$)
= amount (mg) of Norgestrel Reference Standard
$\times \frac{Q_{Ta}}{Q_{Sa}} \times \frac{1}{50}$

Amount (mg) of ethinylestradiol ($C_{20}H_{24}O_2$)
= amount (mg) of Ethinylestradiol Reference Standard
$\times \frac{Q_{Tb}}{Q_{Sb}} \times \frac{1}{50}$

Internal standard solution—A solution of diphenyl in diluted methanol (7 in 10) (1 in 50,000).

Operating conditions—

Detector: Norgestrel—An ultraviolet absorption photometer (wavelength: 241 nm).

Ethinylestradiol—A fluorophotometer (excitation wavelength: 281 nm, fluorescence wavelength: 305 nm.)

Column: A stainless steel column about 4 mm in inside diameter and about 25 cm in length, packed with octadecylsilanized silica gel for liquid chromatography.

Column temperature: Room temperature.

Mobile phase: A mixture of acetonitrile and water (11:9).

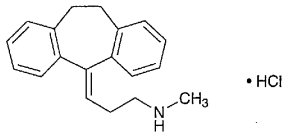
Flow rate: Adjust the flow rate so that the retention time of norgestrel is about 10 minutes.

Selection of column: Proceed with 20 μL of the standard solution under the above operating conditions. Use a column giving elution of ethinylestradiol, norgestrel and the internal standard in this order, and separating clearly each peak.

Containers and storage Containers—Tight containers.

Nortriptyline Hydrochloride

塩酸ノルトリプチリン



$C_{19}H_{21}N.HCl$: 299.84

N-[3-(10,11-Dihydro-5*H*-dibenzo[*a*,*d*]cycloheptен-5-ylidene)propyl]-*N*-methylamine monohydrochloride [*894-71-3*]

Nortriptyline Hydrochloride, when dried, contains not less than 98.5% of $C_{19}H_{21}N.HCl$.

Description Nortriptyline Hydrochloride occurs as a white to yellowish white, crystalline powder. It is odorless, or has a faint, characteristic odor.

It is freely soluble in acetic acid (100) and in chloroform, soluble in ethanol (95), sparingly soluble in water, and practically insoluble in diethyl ether.

The pH of a solution of Nortriptyline Hydrochloride (1 in 100) is about 5.5.

Melting point: 215 - 220°C

Identification (1) To 5 mL of a solution of Nortriptyline Hydrochloride (1 in 100) add 1 mL of bromine TS: the color of the test solution disappears.

(2) To 5 mL of a solution of Nortriptyline Hydrochloride (1 in 100) add 1 to 2 drops of a solution of quinhydrone in methanol (1 in 40): a red color gradually develops.

(3) Determine the absorption spectrum of a solution of Nortriptyline Hydrochloride (1 in 100,000) as directed under the Ultraviolet-visible Spectrophotometry, and compare the spectrum with the Reference Spectrum: both spectra exhibit similar intensities of absorption at the same wavelengths.

(4) Determine the infrared absorption spectrum of Nortriptyline Hydrochloride, previously dried, as directed in the potassium chloride disk method under the Infrared Spectrophotometry, and compare the spectrum with the Reference Spectrum: both spectra exhibit similar intensities of absorption at the same wave numbers.

(5) A solution of Nortriptyline Hydrochloride (1 in 100) responds to the Qualitative Tests for chloride.

Purity (1) Clarity and color of solution—Dissolve 0.10 g of Nortriptyline Hydrochloride in 10 mL of water: the solution is clear and colorless to very light yellow.

(2) Heavy metals—Proceed with 1.0 g of Nortriptyline Hydrochloride according to Method 2, and perform the test. Prepare the control solution with 2.0 mL of Standard Lead Solution (not more than 20 ppm).

(3) Arsenic—Prepare the test solution with 1.0 g of Nortriptyline Hydrochloride according to Method 3, and perform the test using Apparatus B (not more than 2 ppm).

(4) Related substances—Dissolve 0.50 g of Nortriptyline Hydrochloride in 20 mL of chloroform, and use this solution as the sample solution. Pipet 2 mL of the sample solution, and add chloroform to make exactly 100 mL. Pipet 5 mL of this solution, add chloroform to make exactly 50 mL, and use this solution as the standard solution. Perform the test with these solutions as directed under the Thin-layer Chromatography. Spot 4 μL each of the sample solution and the standard solution on a plate of silica gel with fluorescent indicator for thin-layer chromatography. Develop the plate with a mixture of cyclohexane, methanol and diethylamine (8:1:1) to a distance of about 15 cm, and air-dry the plate. Examine under ultraviolet light (main wavelength: 254 nm): the spots other than the principal spot from the sample solution are not more intense than the spot from the standard solution.

Loss on drying Not more than 0.5% (1 g, 105°C, 2 hours).

Residue on ignition Not more than 0.10% (1 g).

Assay Weigh accurately about 0.5 g of Nortriptyline Hydrochloride, previously dried, dissolve in 5 mL of acetic acid (100), add 50 mL of acetic anhydride, and titrate with 0.1 mol/L perchloric acid VS (potentiometric titration). Perform a blank determination, and make any necessary correction.

Each mL of 0.1 mol/L perchloric acid VS
= 29.984 mg of $C_{19}H_{21}N.HCl$

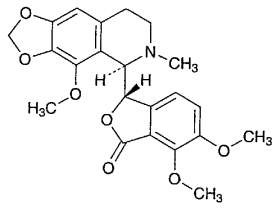
Containers and storage Containers—Well-closed containers.

Storage—Light-resistant.

Noscapine

Narcotine

ノスカピン



$C_{22}H_{23}NO_7$: 413.42

(3*S*)-6,7-Dimethoxy-3-[(5*R*)-5,6,7,8-tetrahydro-4-methoxy-6-methyl[1,3]dioxolo[4,5-*g*]isoquinolin-5-yl]isobenzofuran-1(3*H*)one [*128-62-1*]

Noscapine, when dried, contains not less than 98.5% of $C_{22}H_{23}NO_7$.