Ethinylestradiol and levonorgestrel tablets (Ethinylestradioli et levonorgestreli compressi)

2018-01

Category. Contraceptive.

Storage. Ethinylestradiol and levonorgestrel tablets should be kept in well-closed containers, protected from light.

Additional information. Strengths in the current WHO Model list of essential medicines: 150 µg Levonorgestrel and 30 µg Ethinylestradiol.

The tablets may be coated.

Requirements

Comply with the monograph for "Tablets".

For Ethinylestradiol and levonorgestrel tablets presented in 21-day or 28-day calendar packs, specify the requirements separately for each combination containing different proportions of the active ingredients. Where applicable disregard any tablets that contain no active ingredient (placebo tablets).

Definition. Ethinylestradiol and levonorgestrel tablets contain Ethinylestradiol and Levonorgestrel. They contain not less than 90.0% and not more than 110.0% of the amounts of ethinylestradiol ($C_{20}H_{24}O_2$) and levonorgestrel ($C_{21}H_{28}O_2$) stated on the label.

Identity tests

-Either test A or test B may be applied.

A. Carry out test A.1 or, where UV detection is not available, test A.2.

A.1 Carry out the test as described under *1.14.1 Chromatography*, Thin-layer chromatography, using silica gel R1 as the coating substance and a mixture of 70 volumes of cyclohexane R and 30 volumes of acetone R as the mobile phase. Apply separately to the plate 10 µl of each of the following three solutions. For solution (A) add 1 mL of dichloromethane R to a quantity of the powdered tablets containing about 100 µg of Levonorgestrel and about 60 µg of Ethinylestradiol, shake and filter. For solution (B) use about 100 µg of levonorgestrel RS per mL in dichloromethane R. For solution (C) use about 60 µg of ethinylestradiol RS per mL in dichloromethane R. After removing the plate from the chromatographic chamber, allow it to dry in air. Spray the plate with 4-toluenesulfonic acid/ethanol TS, and heat at 110 °C for 10 minutes. Examine the chromatogram in ultraviolet light (365 nm).

One of the principal spots in the chromatogram obtained with solution A corresponds in position, appearance and intensity to that obtained with solution B and the other principal spot corresponds to that obtained with solution C.

A.2 Carry out the test as described under *1.14.1 Chromatography*, Thin-layer chromatography, using the conditions given under test A.1. Examine the chromatogram in daylight.

One of the principal spots in the chromatogram obtained with solution A corresponds in position, appearance and intensity to that obtained with solution B and the other principal spot corresponds to that obtained with solution C.

B. See the test described below under Assay, method A. The retention times of the principal peaks in the chromatogram obtained with solution (1) are similar to those in the chromatogram obtained with solution (2).

Dissolution

Carry out the test as described under 5.5 Dissolution test for solid oral dosage forms, using 500 mL of 0.1% sodium dodecyl sulfate R in hydrochloric acid (~4 g/l) TS as the dissolution medium, and rotating the paddle at 75 revolutions per minute. At 30 minutes withdraw a sample of about 15 mL of the dissolution medium through an inline filter, discarding the first 10 mL of the filtrate (solution (1)). For solution (2) transfer 1 mL of the solution (2) obtained from the Assay, method A to a 100 mL volumetric flask and make up to volume with the dissolution medium.

Determine the concentration in solution (1) by carrying out the test as described under *1.14.1 Chromatography*, High-performance liquid chromatography, using the stationary and mobile phase given under Assay, method A.

Operate with a flow rate of 1 mL per minute. As detectors use an ultraviolet spectrophotometer set at a wavelength of 247 nm for levonorgestrel analysis and a spectrofluorometric detector for ethinylestradiol analysis with an excitation wavelength of 285 nm and an emission wavelength of 310 nm.

Inject separately 100 µl each of solutions (1) and (2).

Measure the areas of the peak responses corresponding to levonorgestrel and to ethinylestradiol obtained in the chromatograms from solutions (1) and (2) and calculate the total amount of levonorgestrel ($C_{21}H_{28}O_2$) and ethinylestradiol ($C_{20}H_{24}O_2$) in the medium, using the declared content of $C_{21}H_{28}O_2$ in levonorgestrel RS and the declared content of $C_{20}H_{24}O_2$ in ethinylestradiol RS.

For uncoated and film coated tablets. For each of the six tablets tested the amounts in solution are not less than 85% of the amount of levonorgestrel and not less than 80% of the amount of ethinylestradiol stated on the label. If for one of the six tablets the amount of levonorgestrel is less than 85% and/or the amount of ethinylestradiol is less than 80%, repeat the test using a further six tablets; the average amounts for all 12 tablets tested are not less than 80% of levonorgestrel and not less than 75% of ethinylestradiol; no tablet releases less than 65% of levonorgestrel and/or less than 60% of ethinylestradiol.

For sugar coated tablets. For each of the six tablets tested the amounts in solution are not less than 65% of the amounts of levonorgestrel and ethinylestradiol stated on the label. If for one of the six tablets the amounts of levonorgestrel and/or ethinylestradiol are less than 65%, repeat the test using a further six tablets; the average amounts for all 12 tablets tested are not less than 60% of levonorgestrel and ethinylestradiol; no tablet releases less than 45% of levonorgestrel and ethinylestradiol.

Assay

-Either method A or method B may be applied.

A. Weigh and powder 20 tablets. Carry out the test as described under *1.14.1 Chromatography*, High-performance liquid chromatography, using a stainless steel column (25 cm × 4.6 mm) packed with particles of silica gel, the surface of which has been modified with chemically-bonded octadecylsilyl group (5 µm).[1] As the mobile phase use a solution prepared by mixing 57 volumes of acetonitrile R and 43 volumes of water R.

Prepare the following solutions using the mobile phase as diluent. For solution (1) transfer an accurately weighed quantity of the powdered tablets containing about 1.5 mg of Levonorgestrel and about 300 µg of Ethinylestradiol to a 50 mL volumetric flask. Add about 40 mL of the mobile phase and shake for 20 minutes, dilute to volume, mix and filter. For solution (2) use a solution containing 30.0 µg of levonorgestrel RS per mL and 6.0 µg of ethinylestradiol RS per mL.

Operate with a flow rate of 1 mL per minute. As a detector use an ultraviolet spectrophotometer set at a wavelength of 215 nm.

Inject 50 µl of solutions (2). The peak for ethinylestradiol is eluted at a retention time of about 5 minutes, and that for levonorgestrel at about 6.7 minutes. The test is not valid unless the resolution factor between the peaks due to ethinylestradiol and levonorgestrel is at least 2.0.

Inject 50 µl of solutions (1).

Measure the areas of the peak responses corresponding to levonorgestrel and ethinylestradiol obtained in the chromatogram from solutions (1) and (2) and calculate the percentage content of $C_{21}H_{28}O_2$ (levonorgestrel) and $C_{20}H_{24}O_2$ (ethinylestradiol) in the tablets, using the declared content of $C_{21}H_{28}O_2$ in levonorgestrel RS and the declared content of $C_{20}H_{24}O_2$ in ethinylestradiol RS.

B. Use the average of the 10 individual results obtained in the test for Uniformity of content.

Uniformity of content

The tablets comply with the test for 5.1 Uniformity of content for single-dose preparations, using the following method of analysis.

Carry out the test described under *1.14.1 Chromatography*, High-performance liquid chromatography , using the chromatographic conditions as described under Assay, method A.

Prepare the following solutions using the mobile phase as diluent. For solution (1) transfer one tablet to a 5 mL volumetric flask. Add about 4 mL of the mobile phase, sonicate to disintegrate the tablet and shake for 20 minutes, dilute to volume, mix and filter. For solution (2) prepare a solution containing about 30.0 µg of levonorgestrel RS per mL and 6.0 µg of ethinylestradiol RS per mL.

Inject 50 µl of solutions (2). The test is not valid unless the resolution factor between the peaks due to levonorgestrel and ethinylestradiol is at least 2.0.

Inject 50 µl of solutions (1).

Measure the areas of the peak responses corresponding to levonorgestrel and ethinylestradiol obtained in the chromatogram from solutions (1) and (2) and calculate the percentage content of $C_{21}H_{28}O_2$ (levonorgestrel) and $C_{20}H_{24}O_2$ (ethinylestradiol) in

each tablet, using the declared content of $C_{20}H_{24}O_2$ in levonorgestrel RS and the declared content of $C_{20}H_{24}O_2$ in ethinylestradiol RS.