Levonorgestrel tablets (Levonorgestreli compressi)

2014-01

Category. Contraceptive.

Storage. Levonorgestrel tablets should be kept in well-closed containers, protected from light.

Additional information. Strength in the current WHO Model list of essential medicines: 30 µg, 750 µg, 1.5 mg.

Requirements

Comply with the monograph for *Tablets*.

Definition. Levonorgestrel tablets contain Levonorgestrel. They contain not less than 90.0% and not more than 110.0% of the amount of 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 *For 750 µg and 1.5 mg tablets.* Carry out the test as described under *1.14.1 Chromatography*, Thin-layer chromatography using silica gel R6 as the coating substance and a mixture of 7 volumes of cyclohexane R and 3 volumes of acetone R as the mobile phase. Apply separately to the plate 10 µL of each of the following two solutions in acetonitrile R. For solution (A) shake a quantity of the powdered tablets containing 1.5 mg of Levonorgestrel with 5 mL, filter and use the clear filtrate. For solution (B) use 0.30 mg of levonorgestrel RS per mL. After removing the plate from the chromatographic chamber allow it to dry exhaustively in air or in a current of cool air. Examine the chromatogram in ultraviolet light at 254 nm.

For 30 µg tablets. Carry out the test as described above for *750 µg and 1.5 mg tablets* but for solution (A) shake a quantity of the powdered tablets containing 60 µg of Levonorgestrel with 2 mL of acetonitrile R, filter and use the clear filtrate. Apply 100 µL of solution (A) and (B) to the plate.

The principal spot obtained with solution A corresponds in position, appearance and intensity to that obtained with solution B.

A.2 Carry out the test as described under *1.14.1 Chromatography*, Thin-layer chromatography using the conditions described under test A.1 but using silica gel R5 as the coating substance. Spray with a mixture of equal volumes of sulfuric acid TS and ethanol (~750 g/L) TS. Heat the plate for a few minutes at 105 °C. Examine the chromatogram in daylight.

The principal spot obtained with solution A corresponds in position, appearance and intensity to that obtained with solution B.

B. See the method described below under ”Assay”, method A. The retention time of the principal peak in the chromatogram obtained with solution (1) is similar to that in the chromatogram obtained with the solution (2).

Dissolution

For 750 µg and 1.5 mg tablets. Carry out the test as described under *5.5 Dissolution test for solid oral dosage forms* using as the dissolution medium, 500 mL of 0.1% solution of sodium dodecyl sulfate R in hydrochloride solution (0.1 mol/L) VS and rotating the paddle at 75 revolutions per minute. At 30 minutes withdraw a sample of 10 mL of the medium through an in-line filter and use the filtrate. Prepare a standard solution as follows: add a suitable volume of ethanol (~750 g/L) TS to dissolve a suitable amount of levonorgestrel RS, then add a suitable volume of the dissolution medium to obtain a concentration of 6 µg per mL.

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

For each of the six tablets calculate the total amount of levonorgestrel ($C_{21}H_{28}O_2$), in the medium, using the declared content of $C_{21}H_{28}O_2$ in levonorgestrel RS. The amount of levonorgestrel in solution for each tablet is not less than 75% (Q) of the amount declared on the label.

For 30 µg tablets. Carry out the test as described above for *750 µg and 1.5 mg tablets* but using 500 mL of hydrochloride solution (0.01 mol/L) VS as the dissolution medium and 500 µL as the injected volume.

Related substances

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 groups (5 µm). As the mobile phase use a solution prepared as follows: mix 15 volumes of methanol R, 35 volumes of acetonitrile R and 50 volumes of water R.

Prepare the following solutions in the dissolution solvent prepared by mixing equal volumes of methanol R and water R. For solution (1) transfer a quantity of powdered tablets containing about 0.18 mg of Levonorgestrel, accurately weighed, in 5 mL. Sonicate for 30 minutes, stir vigorously for 15 minutes, centrifuge and use the supernatant liquid. For solution (2) dilute a suitable volume of solution (1) to obtain a concentration of 0.36 µg of Levonorgestrel per mL. For solution (3) use 4 µg of ethinylestradiol RS and 4 µg of levonorgestrel RS per mL.

Operate with a flow rate of 1.2 mL per minute. As a detector use an ultraviolet spectrophotometer set at a wavelength of 220 nm.

Maintain the column temperature at 30 °C.

Inject 100 µL of solution (3). Record the chromatogram for twice the retention time of levonorgestrel (retention time about 26 minutes). The test is not valid unless, in the chromatogram obtained with solution (3), the resolution factor between the peaks due to ethinylestradiol and levonorgestrel is at least 12.

Inject separately 100 µL of each of solutions (1) and (2). Record the chromatogram for twice the retention time of levonorgestrel.

In the chromatogram obtained with solution (1) the area of any peak, other than the principal peak, is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (1.0 %). The sum of the areas of all peaks, other than the principal peak, is not greater than twice the area of the principal peak in the chromatogram obtained with solution (2) (2.0%).

Assay

Either method A or 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 (15 cm × 4.6 mm) packed with particles of silica gel the surface of which has been modified with chemically-bonded octadecylsilyl groups (5 µm).

As the mobile phase use a solution prepared by mixing equal volumes of acetonitrile R and water R.

Prepare the following solutions.

For 750 µg and 1.5 mg tablets. For solution (1) transfer a quantity of the powdered tablets containing about 1.5 mg, accurately weighed, to a stoppered test-tube, add 5.0 mL of the mobile phase, sonicate for 45 minutes, shake for 15 minutes and centrifuge. Dilute a suitable volume to produce a solution containing 6 µg of Levonorgestrel per mL. For solution (2), accurately weigh 12 mg of levonorgestrel RS, dissolve in sufficient mobile phase to produce 100.0 mL and mix. Dilute 5.0 mL of this solution to 100.0 mL with the same solvent.

For 30 µg tablets. Prepare solution (1) as described above for *750 µg and 1.5 mg tablets* but transferring a quantity of powdered tablets containing about 60 µg of Levonorgestrel, accurately weighed.

Operate with a flow rate of 1.3 mL per minute. As a detector use an ultraviolet spectrophotometer set at a wavelength of 220 nm.

Inject 25 µL of solution (2). The peak of levonorgestrel is eluted at a retention time of about 7.9 minutes. The assay is not valid unless the column efficiency, determined for the peak due to levonorgestrel,, is at least 5000 and its symmetry factor is not more than 1.6.

Inject separately 25 µL each of solutions (1) and (2). Measure the areas of the peak responses corresponding to levonorgestrel and calculate the content of levonorgestrel ($C_{21}H_{28}O_2$) in the tablets using the declared content of $C_{21}H_{28}O_2$ in levonorgestrel 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 as described under *1.14.1 Chromatography*, High-performance liquid chromatography using the chromatographic conditions as described under “Assay”, method A.

Prepare the following solutions. For solution (1) transfer one powdered tablet to a stoppered test-tube, add 5.0 mL of the mobile phase, sonicate for 45 minutes，shake for 15 minutes and centrifuge. Dilute a suitable volume to produce a solution containing 6 µg of Levonorgestrel per mL. For solution (2) accurately weigh 12 mg of levonorgestrel RS, dissolve in sufficient mobile phase to produce 100.0 mL and mix. Dilute 5.0 mL of this solution to 100.0 mL with the same solvent.

Inject 25 µL of solution (2). The peak of levonorgestrel is eluted at a retention time of about 7.9 minutes. The assay is not valid unless the column efficiency, determined for the peak due to levonorgestrel, is at least 5000 and its symmetry factor is not more than 1.6.

Inject separately 25 µL each of solutions (1) and (2). Measure the areas of the peak responses corresponding to levonorgestrel and calculate the content of levonorgestrel ($C_{21}H_{28}O_2$) in the tablets using the declared content of $C_{21}H_{28}O_2$ in levonorgestrel RS .