Ulipristal acetate tablets (Ulipristali acetatis compressi)

Category. Oral hormonal contraceptive.

Storage. Ulipristal acetate tablets should be kept in a well-closed container, protected from light.

Additional information. Strength in the current WHO Model List of Essential Medicines (EML): 30 mg Ulipristal acetate per tablet.

Requirements

The tablets comply with the monograph for <u>Tablets</u>.

Definition. Ulipristal acetate tablets contain Ulipristal acetate. They contain not less than 90.0% and not more than 110.0% of the labelled amount of Ulipristal acetate ($C_{30}H_{37}NO_4$).

Identity tests

-Any two of tests A, B or C may be applied.

Carry out the test as described under <u>1.14.1 Chromatography</u>, <u>High-performance liquid chromatography</u>, using the conditions given under "Assay". The retention time of the principal peak in the chromatogram obtained with solution (1) corresponds to the retention time of the peak due to ulipristal acetate in the chromatogram obtained with solution (2).

Carry out as described under <u>1.6 Spectrophotometry in the visible and ultraviolet regions</u>. Use the solution (1) as prepared for "Assay". Dilute 2.0 mL of solution (1) to 20.0 mL with mobile phase. The absorption spectrum of this solution, when observed between 230 nm and 400 nm, exhibits maxima at about 262 nm and 302 nm.

Alternatively, in combination with identity test B, where a diode-array detector is available, record the UV spectrum of the principal peak in the chromatograms with a diode array detector in the range of 230 nm to 400 nm. The UV spectrum of the principal peak in the chromatogram obtained with solution (1) corresponds to the UV spectrum of the peak due to ulipristal acetate in the chromatogram obtained with solution (2).

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

C.1 Carry out as described under <u>1.14.1 Chromatography</u>, Thin-layer chromatography using silica gel R6 as the coating substance and a freshly prepared mixture of 2 volumes of ethyl acetate R and 8 volumes of dichloromethane R as the mobile phase. Apply separately to the plate 2 µL of each of the following two solutions: for solution (A), transfer a quantity of powdered tablets, nominally containing 60 mg of ulipristal acetate, into a 10 mL volumetric flask. Dilute to volume using dehydrated ethanol R. Stir or shake for 15 minutes. For solution (2), use a solution containing 6 mg of ulipristal acetate RS per mL of dehydrated ethanol R. After removing the plate from the chromatographic chamber, allow it to dry in air. Then heat the plate for 5 minutes in an oven at 100 °C. Examine the chromatogram under ultraviolet light (254 nm).

The principal spot in the chromatogram obtained with solution (A) corresponds in position, appearance and intensity with the spot due to ulipristal acetate in the chromatogram obtained with solution (B).

C.2 Carry out the test as described under <u>1.14.1 Chromatography</u>, Thin-layer chromatography, using silica gel R5 as the coating substance and the conditions as described above under test C.1. Spray the plate with a 100 g/L solution of phosphomolybdic acid R in dehydrated ethanol R. Heat the plate in an oven at 100 °C until spots appear (for about 5 minutes). Examine the chromatogram under visible light. The principal spot in the chromatogram obtained with solution (A) corresponds in position, appearance and intensity with the spot due to Ulipristal acetate in the chromatogram obtained with solution (B).

Dissolution. Carry out the test as described under <u>5.5 Dissolution test for oral dosage forms</u>, using as the dissolution medium 900 mL of hydrochloric acid (0.1 mol/L) VS. Rotate the paddle at 50 revolutions per minute. At 15 minutes, withdraw a sample of 10 mL of the medium through an in-line filter and allow the filtered sample to cool to room temperature. Dilute 10.0 mL of this solution to 25.0 mL with the dissolution medium.

Measure the absorbance as described under <u>1.6 Spectrophotometry in the visible and ultraviolet regions</u> of the diluted sample in a cuvette with an optical pathlength of 10 mm at about 309 nm, using the dissolution medium as the blank.

For each of the tablets tested, calculate the total amount of ulipristal acetate ($C_{30}H_{37}NO_4$) in the medium using the absorptivity value of 43.2 for ulipristal acetate ($A_{1}^{1\%}m = 432_{$).

Evaluate the results as described under <u>5.5 Dissolution test for solid dosage forms</u>, Acceptance criteria. The amount of ulipristal acetate released is not less than 80% (Q) of the amount declared on the label.

Related substances. Perform the test using low-actinic glassware. Carry out the test as described under 1.14.1 Chromatography,

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<u>High-performance liquid chromatography</u>, using the conditions given below under "Assay", with the following modifications.

Prepare the following solution in mobile phase: use solution (1) as described under "Assay". For solution (2), dilute 1.0 mL of solution (1) to 100.0 mL. For solution (3), dilute 2.0 mL of solution (2) to 20.0 mL. For solution (4), prepare a solution containing 0.3 mg/mL ulipristal acetate RS and 0.015 mg/mL ulipristal acetate impurity A RS.

As a detector, use an ultraviolet spectrophotometer set at a wavelength of 254 nm.

Inject 10 μ L each of solutions (1), (2), (3) and (4).

The impurities are eluted, if present, at the following relative retentions with reference to ulipristal acetate (retention time about 9.1 minutes): impurity B about 0.66; impurity C about 0.87 and impurity A about 1.05.

The test is not valid unless, in the chromatogram obtained with solution (4), the peak-to-valley ratio between the peaks due to ulipristal acetate and impurity A is at least 3.0. Also, the test is not valid unless, in the chromatogram obtained with solution (3), the peak due to ulipristal acetate is obtained with a signal-to-noise ratio of at least 10.

In the chromatogram obtained with solution (1):

the area of any peak corresponding to impurity B is not greater than 3 times the area of the peak due to ulipristal acetate in the chromatogram obtained with solution (2) (3.0 %);

the area of any peak corresponding to impurity C is not greater than 0.5 times the area of the peak due to ulipristal acetate in the chromatogram obtained with solution (2) (0.5 %);

the area of any other impurity peak is not greater than 0.2 times the area of the peak due to ulipristal acetate in the chromatogram obtained with solution (2) (0.2 %).

The sum of the areas of all impurity peaks is not greater than 3.5 times the area of the peak due to ulipristal acetate in the chromatogram obtained with solution (2) (3.5%). Disregard all peaks with an area of less than the area of the peak due to ulipristal acetate in the chromatogram obtained with solution (3) (0.1%).

Assay

Either test A or test B may be applied.

Perform the test using low-actinic glassware. Carry out the test as described under <u>1.14.1 Chromatography</u>, Liquid <u>chromatography</u>, using a stainless steel column (4.6 mm x 25 cm) packed with particles of silica gel, the surface of which has been modified with chemically-bonded octadecylsilyl groups (5 μ m).

Prepare a phosphate buffer by dissolving 4.76 g of potassium dihydrogen phosphate R in 1000 mL of water R. Adjust the pH to 7.0 with triethylamine R. As the mobile phase, use a mixture of 40 volumes of acetonitrile R, 15 volumes of tetrahydrofuran R and 45 volumes of the phosphate buffer.

Operate with a flow rate of 1.0 mL per minute.

As a detector, use an ultraviolet spectrophotometer set at a wavelength of 305 nm.

Prepare the following solutions in mobile phase: for solution (1), weigh and powder 20 tablets. Transfer a quantity of the powdered tablets, nominally containing 30.0 mg of ulipristal acetate, to a 100 mL volumetric flask. Add 40 mL and sonicate for 5 minutes, cool to room temperature, make up to volume and filter. For solution (2), dissolve 30.0 mg of ulipristal acetate RS in 40 mL using sonication, dilute to 100.0 mL and filter.

Inject 10 µL each of solutions (1) and (2) and record the chromatogram for 2.5 times the retention time of ulipristal acetate.

Measure the areas of the peaks corresponding to ulipristal acetate obtained in the chromatograms of solutions (1) and (2) and calculate the percentage content of ulipristal acetate ($C_{30}H_{37}NO_4$) in the tablets, using the declared content of $C_{30}H_{37}NO_4$ in ulipristal acetate RS.

Perform the test using low-actinic glassware. Weigh and powder 20 tablets. Transfer a quantity of the powdered tablets, nominally containing 30.0 mg of Ulipristal acetate, to a 100 mL volumetric flask. Add 40 mL of methanol R and sonicate for 5 minutes. Cool to room temperature and make up to volume. Dilute 5.0 mL of this solution to 50.0 mL with the same solvent.

Measure the absorbance as described under <u>1.6 Spectrophotometry in the visible and ultraviolet regions</u> of the resulting solution in a cuvette with an optical pathlength of 10 mm at the maximum of about 302 nm.

Calculate the percentage content of $C_{30}H_{37}NO_4$ in the tablets, using the absorptivity value of 48.4 for ulipristal acetate (

$$A_{1\,cm}^{1\%} = 484_{1}$$

Impurities

The impurities limited by the requirements of this monograph include those listed in the monograph on Ulipristal acetate.