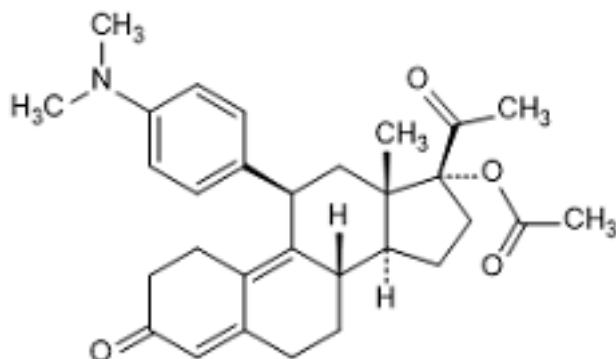


Ulipristal acetate (Ulipristali acetatas)

2022-01

Molecular formula. $C_{30}H_{37}NO_4$ **Relative molecular mass.** 475.63**Graphic formula**

Chemical name. 11 β -[4-(dimethylamino)phenyl]-3,20-dioxopregna-4,9-dien-17-yl acetate (*IUPAC*); 19-Norpregna-4,9-diene-3,20-dione, 17-(acetyloxy)-11-[4-(dimethylamino)phenyl]-, (11 β)-; CAS Reg. No. 126784-99-4.

Description. A white to yellowish crystalline powder.

Solubility. Freely soluble in dichloromethane R; soluble in methanol R, acetone R and dehydrated ethanol R; practically insoluble in water.

Category. Oral hormonal contraceptive.

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

Additional information. Ulipristal acetate exhibits polymorphism.

Requirements

Definition. Ulipristal acetate contains not less than 98.0% and not more than 102.0% of $C_{30}H_{37}NO_4$, calculated with reference to the anhydrous substance.

Identity tests

-Either test A alone, or any two of tests B, C or D may be applied.

Carry out the test as described under [1.7 Spectrophotometry in the infrared region](#). The infrared absorption spectrum is concordant with the spectrum obtained from ulipristal acetate RS.

If the spectra thus obtained are not concordant, repeat the test using the residues obtained by separately dissolving the test substance and ulipristal acetate RS in a small amount of dehydrated ethanol R and evaporating to dryness. The infrared absorption spectrum is concordant with the spectrum obtained from ulipristal acetate RS.

Carry out the test as described under [1.14.1 Chromatography, Liquid chromatography](#), 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).

The absorption spectrum ([1.6 Spectrophotometry in the visible and ultraviolet regions](#)) of a 0.03 mg per mL solution of the test substance in methanol R, 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 D.1 or, where UV detection is not available, test D.2.

D.1 Carry out the test as described under [1.14.1 Chromatography, 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 μ L of each of the following two solutions in dehydrated ethanol R,

containing (A) 6 mg of the test substance per mL and (B) 6 mg of ulipristal acetate RS per mL. 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).

D.2 Carry out the test as described under [1.14.1 Chromatography, Thin-layer chromatography](#), using silica gel R5 as the coating substance and the conditions as described above under test D.1. Spray the plate with a 100 g/L solution of phosphomolybdic acid R in dehydrated ethanol R. Heat the plate at 100 °C in an oven 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).

Specific optical rotation ([1.4](#)). Use a 10 mg per mL solution of the test substance in dioxane R. Calculate with reference to the anhydrous substance; the specific optical rotation $[\alpha]_D^{20}$ is between +156 to +159.

Sulfated ash ([2.3](#)). Not more than 1.0 mg/g, determined on 1.0 g.

Water. Determine, as described under [2.8 Determination of water by the Karl Fischer method](#), Method A. Use 0.500 g of the test substance. The water content is not more than 5 mg/g.

Heavy metals. Use 0.30 g for the preparation of the test solution as described under [2.2.3 Limit test for heavy metals](#), Procedure 5; determine the heavy metals content according to Method C; not more than 10 µg/g.

Related substances. Perform the test using low-actinic glassware. Carry out the test as described under [1.14.1 Chromatography, Liquid chromatography](#), using the conditions given below under "Assay", with the following modifications.

Prepare the following solution in mobile phase: for solution (1), dissolve 30.0 mg of the test substance in 20 mL using sonication and dilute to 50.0 mL. For solution (2), dilute 1.0 mL of solution (1) to 200.0 mL. For solution (3), dilute 2.0 mL of solution (2) to 20.0 mL. For solution (4), prepare a solution containing 0.6 mg/mL ulipristal acetate RS and 0.03 mg/mL ulipristal acetate impurity A RS.

Inject 10 µL 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 signal-to-noise ratio of the peak due to ulipristal acetate is at least 10.

In the chromatogram obtained with solution (1):

the area of any peak corresponding to impurity B is not greater than 1.6 times the area of the peak due to ulipristal acetate in the chromatogram obtained with solution (2) (0.8 %);

the area of any peak corresponding to impurity C is not greater than 0.3 times the area of the peak due to ulipristal acetate in the chromatogram obtained with solution (2) (0.15 %);

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) (0.10 %).

The sum of the areas of all impurity peaks is not greater than twice the area of the peak due to ulipristal acetate in the chromatogram obtained with solution (2) (1.0%). 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) (0.05%).

Assay. Perform the test using low-actinic glassware. Carry out the test as described under [1.14.1 Chromatography, Liquid chromatography](#), 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 µm).

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.

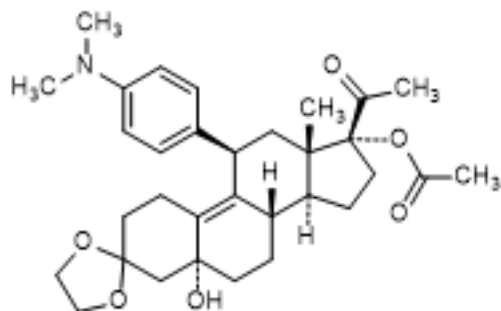
As a detector, use an ultraviolet spectrophotometer set at a wavelength of 254 nm.

Prepare the following solutions in mobile phase: for solution (1), dissolve 30.0 mg of the test substance in 20 mL using sonication and dilute to 50.0 mL. For solution (2), dissolve 30.0 mg of ulipristal acetate RS in 20 mL using sonication and dilute to 50.0 mL.

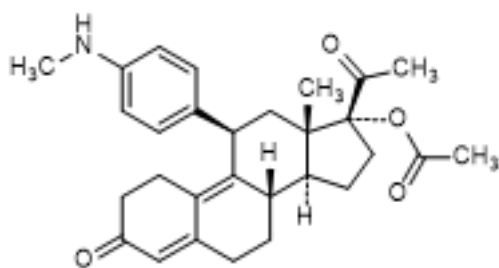
Inject alternately 10 µL each of solutions (1) and (2) and record the chromatogram for 2.5 times the retention time of ulipristal acetate.

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 $C_{30}H_{37}NO_4$ in the sample, using the declared content of $C_{30}H_{37}NO_4$ in ulipristal acetate RS.

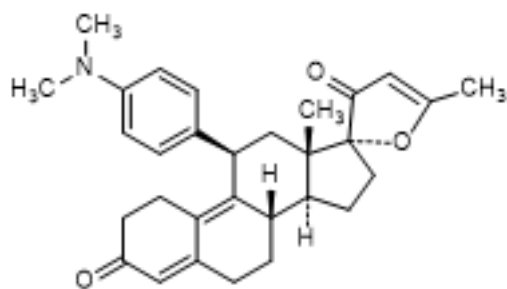
Impurities



A. 11β-[4-(dimethylamino)phenyl]-5'-hydroxy-20'-oxospiro[[1,3]-dioxolane-2,3'-(19'-nor-5'α-pregn-9-en-17-yl)] acetate.



B. 11β-[4-(methylamino)phenyl]-3,20-dioxopregna-4,9-dien-17-yl acetate.



C. (2'R)-11β-[4-(dimethylamino)phenyl]-5'-methylspiro[estrane-17,2'-furane]-4,9-diene-3,3'-dione; (ulipristal cyclopentenone analogue).