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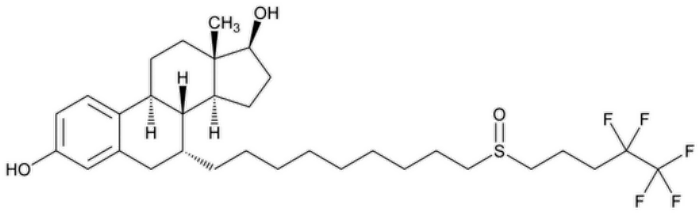
Fulvestrant

Change to read:



$C_{32}H_{47}F_5O_3S$ ▲606.78▲ (ERR 1-Feb-2022)

Estra-1,3,5(10)-triene-3,17-diol, 7-[9-[(4,4,5,5,5-pentafluoropentyl)sulfinyl]nonyl]-, (7α,17β)-;

7α-[9-[(4,4,5,5,5,-Pentafluoropentyl)sulfinyl]non yl]estra-1,3,5(10)-triene-3,17β-diol CAS RN®: 129453-61-8; UNII: 22X328QOC4.

» Fulvestrant is a mixture of the diastereoisomers A and B. It contains not less than 97.0 percent and not more than 102.0 percent of $C_{32}H_{47}F_5O_3S$, calculated on the anhydrous basis.

Packaging and storage—Preserve in well-closed, light-resistant containers. Store refrigerated at 2° to 8°.

USP Reference standards ⟨11⟩—

USP Fulvestrant RS

USP Fulvestrant System Suitability Mixture RS

Contains fulvestrant isomer A, fulvestrant isomer B, and fulvestrant β-isomer.

Identification—

A: *Spectroscopic Identification Tests* ⟨197⟩, *Infrared Spectroscopy: 197K*—

Spectral range: 4000 to 400 cm^{-1}.

B: The retention time of the major peak in the chromatogram of the *Assay preparation* corresponds to that in the chromatogram of the *Standard preparation,* as obtained in the *Assay*.

Specific rotation ⟨781S⟩**:** between +108° and +115° measured at 365 nm.

Test solution: 20 mg per mL, in methanol.

Water Determination, *Method Ic* ⟨921⟩ **:** not more than 0.5%.

Residue on ignition ⟨281⟩**:** not more than 0.1%.

Change to read:

Related compounds—

Mobile phase and *System suitability solution*—Prepare as directed in the *Assay*.

Standard solution—Prepare as directed for the *Standard preparation* in the *Assay*.

Test solution—Use the *Assay preparation*.

Chromatographic system (see *Chromatography* ⟨621⟩)—Proceed as directed in the *Assay*.

Procedure—Separately inject equal volumes (about 10 µL) of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure the peak responses. Calculate the percentage of each impurity in the portion of Fulvestrant taken by the formula:

$$100(CV/W)(1/F)(r_i/r_S)$$

in which C is the concentration, in mg per mL, of USP Fulvestrant RS in the *Standard solution; V* is the volume, in mL, of the *Test solution; W* is the weight, in mg, of Fulvestrant taken to prepare the *Test solution; F* is the relative response factor as listed in the accompanying table; r_i is the individual peak response for each impurity obtained from the *Test solution;* and r_S is the fulvestrant peak response obtained from the *Standard solution*. Disregard impurity peaks less than 0.05%. The limits are as shown in the accompanying table.

Compound	Relative Retention Time	Relative Response Factor	Limit (%)
6-Keto-fulvestrant[1]	0.5	2.9	0.1

Compound	Relative Retention Time	Relative Response Factor	Limit (%)
Δ6,7-Fulvestrant[2]	0.9	3.3	0.1
Fulvestrant	1.0	1.0	—
Fulvestrant sulfone[3]	1.2	1.0	0.2
Fulvestrant extended[4]	1.7	1.0	0.3
Fulvestrant sterol dimer[5]	1.9	1.0	0.8
Fulvestrant β-isomer[6]	1.1	—	*
Any individual unspecified impurity	—	1.0	0.1
Total impurities	—	—	1.0

* Fulvestrant β-isomer, a component of USP Fulvestrant System Suitability Mixture RS, is not a specified impurity.

▲1 7α-{9-[(4,4,5,5,5,-Pentafluoropentyl)sulfinyl]nonyl}estra-1,3,5(10)-triene-6-one-3,17β-diol▲ (ERR 1-Feb-2022)

▲2 7-{9-[(4,4,5,5,5,-Pentafluoropentyl)sulfinyl]nonyl}estra-1,3,5(10),6-tetraene-3,17β-diol▲ (ERR 1-Feb-2022)

▲3 7α-{9-[(4,4,5,5,5,-Pentafluoropentyl)sulfonyl]nonyl}estra-1,3,5(10)-triene-3,17β-diol▲ (ERR 1-Feb-2022)

▲4 7α-{9-[9-[(4,4,5,5,5-pentafluoropentyl)sulfinyl]nonylsulfinyl]nonyl}estra-1,3,5(10)-triene-3,17β-diol▲ (ERR 1-Feb-2022)

▲5 7α,7α-Nonamethylenebis[estra-1,3,5(10)-triene-3,17β-diol]▲ (ERR 1-Feb-2022)

▲6 7β-{9-[(4,4,5,5,5,-Pentafluoropentyl)sulfinyl]nonyl}estra-1,3,5(10)-triene-3,17β-diol▲ (ERR 1-Feb-2022)

Diastereoisomer ratio—

Mobile phase—Prepare a filtered and degassed mixture of 2-methylpentane and dehydrated alcohol (880:120). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

System suitability solution—Dissolve a suitable quantity of USP Fulvestrant System Suitability Mixture RS in *Mobile phase* to obtain a solution containing 1 mg of USP Fulvestrant System Suitability Mixture RS per mL.

Test solution—Transfer about 20 mg of Fulvestrant, accurately weighed, to a 20-mL volumetric flask, dissolve in and dilute with *Mobile phase* to volume, and mix.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 280-nm detector and a 4.6-mm × 25-cm column that contains 10-µm packing L51. The flow rate is about 1 mL per minute. The column temperature is maintained at 40°. Chromatograph the *System suitability solution,* and record the peak responses as directed for *Procedure:* the resolution, *R*, between fulvestrant isomer A and fulvestrant isomer B is not less than 1.3; and the tailing factor for fulvestrant isomer B is not more than 1.5.[Note—For the purpose of peak identification, the retention times are about 20 minutes for fulvestrant isomer B and 23 minutes for fulvestrant isomer A.]

Procedure—Inject a volume (about 10 µL) of the *Test solution* into the chromatograph, record the chromatogram, and measure the responses for the two fulvestrant isomer peaks. Calculate the content of fulvestrant isomer A or fulvestrant isomer B, as a percentage, by the formula:

$$100(r_U/r_S)$$

in which r_U is the peak response of either fulvestrant isomer A or fulvestrant isomer B; and r_S is the total peak response of both fulvestrant isomer A and fulvestrant isomer B: between 42% and 48% of fulvestrant isomer A and between 52% and 58% of fulvestrant isomer B is obtained.

Assay—

Solution A—Prepare a filtered and degassed mixture of water, acetonitrile, and methanol (410:320:270).

Solution B—Prepare a filtered and degassed mixture of acetonitrile, methanol, and water (490:410:100).

Mobile phase—Use variable mixtures of *Solution A* and *Solution B* as directed for *Chromatographic system*. Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

System suitability solution—Dissolve suitable quantities of USP Fulvestrant System Suitability Mixture RS in methanol to obtain a solution containing about 10 mg of USP Fulvestrant System Suitability Mixture RS per mL.

Standard preparation—Dissolve an accurately weighed quantity of USP Fulvestrant RS in methanol to obtain a solution having a known concentration of about 10 mg per mL.

Assay preparation—Transfer about 100 mg of Fulvestrant, accurately weighed, to a 10-mL volumetric flask, dissolve in and dilute with methanol to volume, and mix.

Chromatographic system (see Chromatography ⟨621⟩)—The liquid chromatograph is equipped with a 225-nm detector and a 4.6-mm × 15-cm column that contains 3.5-µm packing L7. The flow rate is about 2 mL per minute. The column temperature is maintained at 40°. The chromatograph is programmed as follows.

Time (minutes)	*Solution A* (%)	*Solution B* (%)	Elution
0–25	100	0	isocratic
25–55	100→0	0→100	linear gradient
55–65	0	100	isocratic
65–66	0→100	100→0	linear gradient
66–70	100	0	equilibration

Chromatograph the *System suitability solution,* and record the peak responses as directed for *Procedure:* the relative retention times are about 1.1 for fulvestrant β-isomer and 1.0 for fulvestrant; the resolution, *R*, between fulvestrant and fulvestrant β-isomer is not less than 1.5; and the tailing factor for the fulvestrant peak is not more than 1.5. Chromatograph the *Standard preparation*, and record the peak responses as directed for *Procedure:* the relative standard deviation for replicate injections is not more than 2.0%.

Procedure—Separately inject equal volumes (about 10 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the responses for the fulvestrant peaks. Calculate the quantity, in mg, of $C_{32}H_{47}F_5O_3S$ in the portion of Fulvestrant taken by the formula:

$$CV(r_U/r_S)$$

in which *C* is the concentration, in mg per mL, of USP Fulvestrant RS in the *Standard preparation; V* is the volume, in mL, of the *Assay preparation;* and r_U and r_S are the peak responses obtained from the *Assay preparation* and the *Standard preparation,* respectively.

Auxiliary Information - Please check for your question in the FAQs before contacting USP.

Topic/Question	Contact	Expert Committee
FULVESTRANT	Documentary Standards Support	SM52020 Small Molecules 5

Chromatographic Database Information: Chromatographic Database

Most Recently Appeared In:
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