Flutamide Capsules

» Flutamide Capsules contain not less than 93.0 percent and not more than 107.0 per cent of the labeled amount of flutamide ($C_{11}H_{11}F_3N_2O_3$).

Packaging and storage—Preserve in well-closed, light-resistant containers.

USP Reference standards ⟨11⟩**—**
USP Flutamide RS

Identification—

A: The retention time of the major peak in the chromatogram of the *Assay preparation* corresponds to that in the chromatogram of the *Standard preparation,* both relative to the internal standard, as obtained in the *Assay.*

B: Remove the contents of 20 Capsules, and grind the contents to a fine powder. Dissolve a portion of the powder in a mixture of chloroform and methanol (5:1) to obtain a solution containing 3 mg of flutamide per mL. The test solution so obtained responds to the *Thin-Layer Chromatographic Identification Test* ⟨201⟩, a mixture of chloroform and ethyl acetate (3:1) being used as the developing solvent and 20 µL each of the test solution and the Standard solution being applied to the thin-layer chromatographic plate.

Dissolution ⟨711⟩**—**

Medium: 2% sodium lauryl sulfate solution; 1000 mL.

Apparatus 2: 75 rpm.

Time: 60 minutes.

Procedure—Determine the amount of $C_{11}H_{11}F_3N_2O_3$ dissolved from UV absorbances at the wavelength of maximum absorbances at the wavelength of maximum absorbance at about 306 nm on filtered portions of the solution under test, suitably diluted with *Dissolution Medium,* in comparison with a Standard solution having a known concentration of USP Flutamide RS in the same *Medium.*

Tolerances—Not less than 75% *(Q)* of the labeled amount of $C_{11}H_{11}F_3N_2O_3$ is dissolved in 60 minutes.

Uniformity of dosage units ⟨905⟩**:** meet the requirements.

Chromatographic purity—

Mobile phase—Prepare as directed in the *Assay.*

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

Test solution—Use the *Assay preparation.*

Detector sensitivity solution—Transfer an accurately measured volume of the *Standard solution* into a volumetric flask, and dilute quantitatively, and stepwise if necessary, with a mixture of water and acetonitrile (4:1) to obtain a solution having a known concentration of about 0.2 µg per mL.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 240-nm detector and a 4.6-mm × 25-cm column that contains packing L1. The column temperature is maintained at 25 ± 5°. The flow rate is about 1.0 mL per minute. Chromatograph the *Detector sensitivity solution,* and record the peak area responses as directed for *Procedure:* the relative standard deviation for replicate injections is not more than 10% for flutamide.

Procedure—Inject a volume (about 20 µL) of the *Test solution* into the chromatograph, record the chromatogram, and measure the peak area responses. Calculate the percentage of each impurity in the portion of Capsules taken by the formula:

$$100(r_i / r_s)$$

in which r_i is the peak area response for each impurity, excluding those where peak area responses are less than those obtained from the *Detector sensitivity solution;* and r_s is the sum of the responses of all the peaks: not more than 0.2% for any impurity having a relative retention time of about 0.45 is found; not more than 0.1% of any other impurity is found; and not more than 0.3% of total impurities is found.

Assay—

Diluent—Prepare a mixture of acetonitrile and water (1:1).

Mobile phase—Prepare a filtered and degassed mixture of water and acetonitrile (55:45). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Standard preparation—Dissolve an accurately weighed quantity of USP Flutamide RS in *Diluent,* and dilute quantitatively, and stepwise if necessary, with *Diluent* to obtain a solution having a known concentration of about 0.5 mg per mL. Transfer 20.0 mL of this solution into a 50-mL volumetric flask, and dilute with water to volume to obtain a final concentration of 0.2 mg per mL.

Assay preparation—Remove the contents of not fewer than 20 Capsules, and mix. Transfer an accurately weighed portion of the powder, equivalent to 125 mg of flutamide, into a 250-mL volumetric flask. Add 180 mL of *Diluent.* Shake the flask for 15 minutes. Dilute with *Diluent* to volume, and mix. Allow the insoluble material to settle. Transfer 20.0 mL of supernatant into a 50-mL volumetric flask, dilute with water to volume, mix, and pass through a polytef membrane filter having a 0.45-µm porosity.

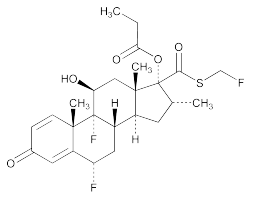
Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 240-nm detector and a 4.6-mm × 25-cm column that contains packing L1. The column temperature is maintained at 25 ± 5°. The flow rate is about 1.0 mL per minute. Chromatograph the *Standard preparation,* and record the peak area response as directed for *Procedure:* the tailing factor is not more than 2.0; and the relative standard deviation for replicate injections is not more than 1.5%.

Procedure—Separately inject equal volumes (about 20 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the peak area response for the flutamide peak. Calculate the quantity, in mg, of flutamide ($C_{11}H_{11}F_3N_2O_3$) in the portion of Capsules taken by the formula:

$$625C(r_U / r_S)$$

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

Fluticasone Propionate



$C_{25}H_{31}F_3O_5S$ 500.57

Androsta-1,4-diene-17-carbothioic acid, 6,9-difluoro-11-hydroxy-16-methyl-3-oxo-17-(1-oxopropoxy)-, (6α,11β,16α,17α)-*S*-(fluoromethyl) ester;

S-Fluoromethyl 6α,9α-difluoro-11β-hydroxy-16α-methyl-3-oxo-17α-propionyloxyandrosta-1,4-diene-17β-carbothioate [80474-14-2].

DEFINITION

Fluticasone Propionate contains NLT 98.0% and NMT 101.0% of $C_{25}H_{31}F_3O_5S$, calculated on the anhydrous, solvent-free basis.

IDENTIFICATION

- **A. INFRARED ABSORPTION** ⟨197M⟩
- **B.** The retention time of the major peak of the *Sample solution* corresponds to that of the *Standard solution*, as obtained in the *Assay*.

ASSAY

- **PROCEDURE**

Buffer: 1.15 g/L of monobasic ammonium phosphate, adjusted with phosphoric acid to a pH of 3.5 ± 0.05
Mobile phase: Methanol, acetonitrile, and *Buffer* (50:15:35)
System suitability solution: 0.05 mg/mL of USP Fluticasone Propionate Resolution Mixture RS in *Mobile phase*
Standard solution: 0.04 mg/mL of USP Fluticasone Propionate RS in *Mobile phase*
Sample solution: 0.04 mg/mL of Fluticasone Propionate in *Mobile phase*
Chromatographic system
(See *Chromatography* ⟨621⟩, *System Suitability*.)
Mode: LC
Detector: UV 239 nm
Column: 4.6-mm × 25-cm; 5-µm packing L1
Column temperature: 40°
Flow rate: 1.5 mL/min
Injection size: 20 µL
System suitability
Samples: *System suitability solution* and *Standard solution*
[NOTE—The relative retention times for fluticasone propionate and fluticasone propionate related compound D are about 1.0 and 1.10, respectively.]
Suitability requirements
Resolution: NLT 1.5 between fluticasone propionate and fluticasone propionate related compound D, *System suitability solution*
Relative standard deviation: NMT 2%, *Standard solution*
Analysis
Samples: *Standard solution* and *Sample solution*
Calculate the percentage of fluticasone propionate ($C_{25}H_{31}F_3O_5S$) in the portion of Fluticasone Propionate taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times 100$$

r_U = peak response of fluticasone propionate from the *Sample solution*
r_S = peak response of fluticasone propionate from the *Standard solution*
C_S = concentration of USP Fluticasone Propionate RS in the *Standard solution* (mg/mL)
C_U = concentration of Fluticasone Propionate in the *Sample solution* (mg/mL)

Acceptance criteria: 98.0%–101.0% on the anhydrous, solvent-free basis

IMPURITIES

- **ORGANIC IMPURITIES**

Solution A: 0.5 mL of phosphoric acid in 1000 mL of acetonitrile
Solution B: 0.5 mL of phosphoric acid in 1000 mL of methanol
Solution C: 0.5 mL of phosphoric acid in 1000 mL of water
Mobile phase: See *Table 1*.

Table 1

Time (min)	Solution A (%)	Solution B (%)	Solution C (%)
0	42	3	55
40	53	3	44
60	87	3	10
70	87	3	10
75	42	3	55

System suitability solution: Dissolve 2.0 mg of USP Fluticasone Propionate System Suitability Mixture RS in 5 mL of *Solution A* using sonication. Add 5 mL of *Solution C*.
Sample solution: 2.0 mg/mL prepared as follows: Dissolve 2.0 mg of Fluticasone Propionate in 5 mL of *Solution A* using sonication. Add 5 mL of *Solution C*.
Chromatographic system
(See *Chromatography* ⟨621⟩, *System Suitability*.)
Mode: LC
Detector: UV 239 nm
Column: 4.6-mm × 25-cm; 5-µm packing L1
Column temperature: 40°
Flow rate: 1 mL/min
Injection size: 50 µL
System suitability
Sample: *System suitability solution*
Suitability requirements
Resolution: NLT 0.6 between fluticasone propionate related compound B and fluticasone propionate related compound C; NLT 1.5 between fluticasone propionate related compound D and fluticasone propionate
Analysis
Sample: *Sample solution*
Calculate the percentage of each impurity in the portion of Fluticasone Propionate taken:

$$\text{Result} = (r_U/r_T) \times 100$$

r_U = peak response for each impurity
r_T = sum of the responses of all the peaks

Acceptance criteria: See *Table 2*.

Table 2

Name	Relative Retention Time	Acceptance Criteria, NMT (%)
Fluticasone propionate related compound A	0.5	0.2
Fluticasone propionate related compound B	0.75	0.1
Fluticasone propionate related compound C	0.8	0.1
Fluticasone propionate related compound D	0.95	0.3
Fluticasone propionate	1.0	—
Fluticasone propionate related compound E	1.3	0.3
Any individual unspecified impurity	—	0.1
Total impurities*	—	1.0

* Include all impurity peaks greater than or equal to 0.05%.

- **LIMIT OF ACETONE**

Internal standard solution: 0.05% (v/v) solution of tetrahydrofuran in dimethylformamide
Standard solution: 0.05% (v/v) of acetone in *Internal standard solution*
Sample solution: 50 mg/mL of Fluticasone Propionate in the *Internal standard solution*
Chromatographic system
(See *Chromatography* ⟨621⟩, *System Suitability*.)

Mode: GC
Detector: Flame ionization
Column: 0.53-mm × 25-m; 2-µm film of phase G16
Carrier gas: Nitrogen or helium
Temperature
Detector: 250°
Splitless injector: 150°
Column: See *Table 3*.

Table 3

Initial Temperature (°)	Temperature Ramp (°/min)	Final Temperature (°)	Hold Time at Final Temperature (min)
60	0	60	3.5
60	30	180	3.0

Flow rate: 5.5 mL/min
Injection size: 0.1 µL
System suitability
Sample: *Standard solution*
Suitability requirements
Relative standard deviation: NMT 5.0%
Analysis
Samples: *Standard solution* and *Sample solution*
Calculate the percentage of acetone (w/w) in the portion of Fluticasone Propionate taken:

$$\text{Result} = (R_U/R_S) \times D \times (C_S/C_U)$$

R_U = peak response ratio of acetone to tetrahydrofuran from the *Sample solution*
R_S = peak response ratio of acetone to tetrahydrofuran from the *Standard solution*
D = density of acetone at 20 ° (g/mL)
C_S = concentration of acetone in the *Standard solution* (%v/v)
C_U = concentration of Fluticasone Propionate in the *Sample solution* (g/mL)
Acceptance criteria: NMT 1.0% (w/w)

SPECIFIC TESTS

- **Optical Rotation,** *Specific Rotation* ⟨**781S**⟩**:** +32° to +36° at 20°, calculated on the anhydrous, solvent-free basis
Sample solution: 0.5% (w/v) of Fluticasone Propionate in dichloromethane (0.5 g in 100 mL)
- **Water Determination,** *Method I* ⟨**921**⟩**:** NMT 0.2% (w/w)

ADDITIONAL REQUIREMENTS

- **Packaging and Storage:** Preserve in tight, light-resistant containers, and store at a temperature not exceeding 30 °.
- **Labeling:** Fluticasone Propionate in the form of microcrystals is so labeled.
- **USP Reference Standards** ⟨**11**⟩
USP Fluticasone Propionate RS
USP Fluticasone Propionate Resolution Mixture RS
USP Fluticasone Propionate System Suitability Mixture RS
It is a mixture of USP Fluticasone Propionate RS and fluticasone propionate related compounds B, C, and D.
Fluticasone propionate related compound A: 6α,9α-Difluoro-11β-hydroxy-16α-methyl-3-oxo-17α-propionyloxyandrosta-1,4-diene-17β-carbonylsulfenic acid.
Fluticasone propionate related compound B: 6α,9α-Difluoro-11β-hydroxy-16α-methyl-2′,3,4′-trioxo-17α-spiro(androsta-1,4-diene-17,5′-(1,3)oxathiolane).
Fluticasone propionate related compound C: S-Fluoromethyl 17α-acetyloxy-6α,9α-difluoro-11β-hydroxy-16α-methyl-3-oxo-androsta-1,4-diene-17β-carbothioate.
Fluticasone propionate related compound D: S-Methyl 6α,9α-difluoro-11β-hydroxy-16α-methyl-3-oxo-17α-propionyloxy-androsta-1,4-diene-17β-carbothioate.
Fluticasone propionate related compound E: 6α,9α-Difluoro-11β,17α-dihydroxy-16α-methyl-3-oxo-androsta-1,4-diene-17β-carboxylic acid 6α,9α-difluoro-17β-(fluoromethylthio) carbonyl-11β-hydroxy-16α-methyl-3-oxo-androsta-1,4-dien-17α-yl ester.

Fluticasone Propionate Cream

DEFINITION

Fluticasone Propionate Cream contains NLT 90.0% and NMT 110.0% of the labeled amount of fluticasone propionate ($C_{25}H_{31}F_3O_5S$).

IDENTIFICATION

- **A. Thin-Layer Chromatographic Identification Test** ⟨**201**⟩
Standard solution: 0.4 mg/mL of USP Fluticasone Propionate RS in acetonitrile
Test solution: Transfer a quantity of Cream, equivalent to 1000 µg of fluticasone propionate, to a 125-mL separatory funnel. Add 25 mL of acetonitrile and 25 mL of hexane to the separatory funnel. Stopper and shake the funnel until the Cream is completely dispersed. Shake the separatory funnel for an additional 3 min, and allow the phases to separate. Filter the lower layer through a 20-mL syringe containing a cotton plug into a 50-mL volumetric flask. Repeat the extraction with one 7-mL aliquot of acetonitrile, and filter the lower layer into the volumetric flask. Wash the cotton plug with 2 mL of acetonitrile, and collect the washings into the volumetric flask. Dilute the sample extract with acetonitrile to volume. Transfer 12 mL of the sample extract to a glass tube suitable for evaporation, and evaporate to dryness at about 40°. Dissolve the residue in 0.6 mL of acetonitrile. [NOTE—The *Test solution* may be cloudy because of the presence of undissolved excipients.]
Chromatographic system
(See *Chromatography* ⟨621⟩*, Thin-Layer Chromatography*.)
Adsorbent: 0.2-mm layer of chromatographic silica gel mixture on a high-performance thin-layer chromatographic plate, 5-µm particle size
Application volume: 40 µL
Developing solvent system: Dichloromethane, ethyl acetate, and glacial acetic acid (30:8:1)
Analysis
Samples: *Standard solution* and *Test solution*
Separately apply the *Standard solution* and the *Test solution* to the plate. On the same plate, apply 20 µL of the *Standard solution,* allow the application to dry, and apply 20 µL of the *Test solution* on top of the dried 20- µL *Standard solution* spot. Allow each of the applications to dry thoroughly. Place the plate in a tank equilibrated with the developing solvent, and allow the developing solvent to travel about 8 cm from the point of application. Remove the plate and allow to air-dry. Examine the plate under ultraviolet light at 254 nm.
Acceptance criteria: The R_F value of the principal spot from the *Test solution* corresponds to that of the *Standard solution*. [NOTE—If the excipients in the Cream interfere with the appearance of the principal spot obtained for the *Test solution*, use the *Standard solution* and the *Test solution* overspot to confirm identity.]
- **B.** The retention time of the major peak of the *Sample solution* corresponds to that of the *Standard solution*, as obtained in the *Assay*.

ASSAY

- **Procedure**
[NOTE—Protect the *Standard solution* and the *Sample solution* from direct light by using a light-protective volumetric flask and autosampler vials.]
Buffer: 1.2 g/L of monobasic ammonium phosphate. Adjust with phosphoric acid to a pH of 3.50 ± 0.03.
Mobile phase: Methanol, acetonitrile, and *Buffer* (46:14:40)
Diluent: Alcohol and water (65:35)
System suitability stock solution: 0.5 mg/mL of USP Fluticasone Propionate Nasal Spray Resolution Mixture RS in