Dutasteride

Type of Posting	Revision Bulletin
Posting Date	29-Dec-2017
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Expert Committee	Chemical Medicines Monographs 5
Reason for Revision	Compliance

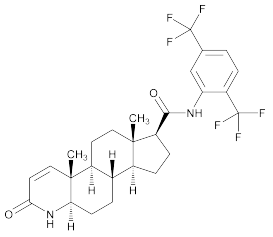
In accordance with the Rules and Procedures of the 2015-2020 Council of Experts, the Chemical Medicines Monographs 5 Expert Committee has revised the Dutasteride monograph.

The purpose of this revision is to widen the limit for the hydrate form of dutasteride from NMT 1.5% to NMT 2.0%, to accommodate the sponsor's FDA approved specification. Text is added to indicate that <921> *Methods Ia* and *Ic* could be used for the hydrate form.

The Dutasteride Revision Bulletin supersedes the currently official monograph. The Revision Bulletin will be incorporated into the *Second Supplement* to *USP 41–NF 36*.

Should you have any questions, please contact Mary Koleck, Ph.D., Scientific Liaison (301-230-7420 or mpk@usp.org.)

Dutasteride



$C_{27}H_{30}F_6N_2O_2$ 528.53

(5α,17β)-*N*-[2,5-Bis(trifluoromethyl)phenyl]-3-oxo-4-azaandrost-1-ene-17-carboxamide;
α,α,α,α′,α′,α′-Hexafluoro-3-oxo-4-aza-5α-androst-1-ene-17β-carboxy-2′,5′-xylidide [164656-23-9].

DEFINITION

Dutasteride contains NLT 97.0% and NMT 102.0% of dutasteride ($C_{27}H_{30}F_6N_2O_2$), calculated on the anhydrous and solvent-free basis.

IDENTIFICATION

- **A. INFRARED ABSORPTION ⟨197K⟩ or ⟨197M⟩:** ⟨197A⟩ may be used.
- **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**

Diluent: Acetonitrile and water (60:40)
Mobile phase: Acetonitrile, water, and trifluoroacetic acid (52: 48: 0.025)
System suitability solution: 0.5 mg/mL of USP Dutasteride Resolution Mixture RS in *Diluent*. Sonicate to dissolve.
Standard solution: 0.5 mg/mL of USP Dutasteride RS in *Diluent*. Sonicate to dissolve.
Sample solution: 0.5 mg/mL of Dutasteride in *Diluent*. Sonicate to dissolve.
Chromatographic system
(See *Chromatography* ⟨621⟩, *System Suitability*.)
Mode: LC
Detector: UV 220 nm
Column: 4.6-mm × 25-cm; 5-µm packing L1
Column temperature: 35°
Flow rate: 1 mL/min
Injection volume: 10 µL
Run time: 1.5 times the retention time of dutasteride
System suitability
Samples: *System suitability solution* and *Standard solution*
[NOTE—See *Table 3* for the relative retention times.]
Suitability requirements
Resolution: NLT 1.5 between dutasteride 17α-epimer and dutasteride, *System suitability solution*
Relative standard deviation: NMT 1.5%, *Standard solution*
Analysis
Samples: *Standard solution* and *Sample solution*
Calculate the percentage of dutasteride ($C_{27}H_{30}F_6N_2O_2$) in the portion of Dutasteride taken:

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

r_U = peak response from the *Sample solution*
r_S = peak response from the *Standard solution*
C_S = concentration of USP Dutasteride RS in the *Standard solution* (mg/mL)
C_U = concentration of Dutasteride in the *Sample solution* (mg/mL)
Acceptance criteria: 97.0%–102.0% on the anhydrous and solvent-free basis

IMPURITIES

- **RESIDUE ON IGNITION ⟨281⟩:** NMT 0.1%
- **LIMIT OF PLATINUM**

[NOTE—Perform this test only if platinum is a known inorganic impurity of the manufacturing process.]
Diluent: Hydrochloric acid and dimethyl sulfoxide (2:98). Prepare in a plastic volumetric flask.
Standard stock solution: 10 µg/mL of platinum in *Diluent*. Prepare by diluting (1:100) a 1000-µg/mL commercially available platinum standard.
Standard solution 1: 1.0 µg/mL of platinum in *Diluent* from the *Standard stock solution*
Standard solution 2: 0.1 µg/mL of platinum in *Diluent* from *Standard solution 1*
Sample solution: 0.01 g/mL of Dutasteride in *Diluent*. Sonicate to dissolve.
Instrumental conditions
(See *Plasma Spectrochemistry* ⟨730⟩.)
Mode: ICP–OES
Analytical wavelength: 306.471 nm
Spectrophotometric system: Use an inductively coupled plasma–optical emission spectrophotometric system, and construct a calibration curve using the response from the *Diluent*, *Standard solution 1*, and *Standard solution 2*.
System suitability
Samples: *Diluent*, *Standard solution 1*, and *Standard solution 2*
Suitability requirements
Limit of quantitation: 3 µg/g for platinum
Calculate the limit of quantitation from the *Diluent*:

$$\text{Result} = 10 \times (SD/C_S)$$

SD = standard deviation of platinum from *Diluent* (µg/mL)
C_S = nominal concentration of dutasteride in the *Sample solution* (g/mL)
Correlation coefficient: NLT 0.99 from the *Diluent*, *Standard solution 1*, and *Standard solution 2*
Analysis
Samples: *Diluent*, *Standard solution 1*, *Standard solution 2*, and *Sample solution*
Plot the responses of the *Diluent*, *Standard solution 1*, and *Standard solution 2* versus their content (0, 0.1, and 1.0 µg/mL) of platinum. Determine the concentration, in µg/mL, of platinum in the *Sample solution* from the calibration curve.
Calculate the concentration, in µg/g, of platinum in the portion of Dutasteride taken:

$$\text{Result} = C_S/C_U$$

C_S = concentration of platinum in the *Sample solution* (µg/mL)
C_U = concentration of Dutasteride in the *Sample solution* (g/mL)
Acceptance criteria: NMT 5 µg/g

- **LIMIT OF RESIDUAL SOLVENTS**

Standard stock solution: 5 mg/mL each of acetonitrile, ethyl acetate, pyridine, toluene, dioxane, and *n*-heptane in dimethyl sulfoxide
Standard solution: 10 µg/mL each of acetonitrile, ethyl acetate, pyridine, toluene, dioxane, and *n*-hep-

tane in dimethyl sulfoxide from the *Standard stock solution*
Sample solution: 10 mg/mL of Dutasteride in dimethyl sulfoxide
Chromatographic system
(See *Chromatography* ⟨621⟩, *System Suitability*.)
Mode: GC
Detector: Flame ionization
Column: 0.32-mm × 30-m; capillary coated with 5-µm film of phase G1
Temperatures
Injection port: 180°
Detector: 260°
Column: See *Table 1*.

Table 1

Initial Temperature (°)	Temperature Ramp (°/min)	Final Temperature (°)	Hold Time at Final Temperature (min)
50	—	50	3
50	10	200	2

Carrier gas: Helium
Flow rate: Head pressure at 12 psi
Split flow: 10 mL/min
Septum purge: 2 mL/min
Injector type: Headspace
Sample volume: 2 mL
Temperatures
Sample: 85°
Needle: 100°
Transfer line: 110°
Times
Equilibration: 1 min
Thermostating: 15 min
System suitability
Sample: *Standard solution*
Suitability requirements
Resolution: NLT 1.2 between *n*-heptane and dioxane peaks
Relative standard deviation: NMT 5% for each solvent
Analysis
Samples: *Standard solution* and *Sample solution*
Calculate the percentage of each solvent in the portion of Dutasteride taken:

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

r_U = peak response of each solvent from the *Sample solution*
r_S = peak response of each solvent from the *Standard solution*
C_S = concentration of each solvent in the *Standard solution* (mg/mL)
C_U = concentration of Dutasteride in the *Sample solution* (mg/mL)
Acceptance criteria: See *Table 2*.

Table 2

Name	Relative Retention Time	Acceptance Criteria, NMT (%)
Acetonitrile	0.30	0.3
Ethyl acetate	0.60	0.2
Dioxane	0.83	0.1

Table 2 *(Continued)*

Name	Relative Retention Time	Acceptance Criteria, NMT (%)
n-Heptane	0.85	0.5
Pyridine	0.92	0.2
Toluene	1.0	0.2

• **ORGANIC IMPURITIES, PROCEDURE 1**
Diluent, Mobile phase, System suitability solution, Sample solution, and **Chromatographic system:** Proceed as directed in the *Assay*.
System suitability
Sample: *System suitability solution*
[NOTE—See *Table 3* for the relative retention times.]
Suitability requirements
Resolution: NLT 1.5 between dutasteride 17α-epimer and dutasteride
Analysis
Sample: *Sample solution*
Calculate the percentage of each impurity in the portion of Dutasteride taken:

$$\text{Result} = (r_U/r_T) \times (1/F) \times 100$$

r_U = peak area for each impurity from the *Sample solution*
r_T = sum of all the peak areas from the *Sample solution*
F = relative response factor (see *Table 3*)
Acceptance criteria: See *Table 3*.

Table 3

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
Dutasteride acid[a]	0.10	1.0	0.2
Dutasteride dimethylamide[b]	0.11	1.4	0.2
Dutasteride methyl ester[c]	0.28	1.0	0.15
Dutasteride ethyl ester[d]	0.39	1.0	0.2
Dutasteride 17α-5-ene[e]	0.90	1.0	0.2
Dutasteride 17α-epimer	0.93	1.0	0.3
Dutasteride	1.00	—	—
Chlorodutasteride[f]	1.15	0.33	0.4
Dutasteride 5-ene[g]	1.20	1.0	0.3
Any other individual impurity	—	—	0.1

[a] (5α,17β)-3-Oxo-4-azaandrost-1-ene-17-carboxylic acid.
[b] (5α,17β)-*N*,*N*-Dimethyl-3-oxo-4-azaandrost-1-ene-17-carboxamide.
[c] Methyl (5α,17β)-3-oxo-4-azaandrost-1-ene-17-carboxylate.
[d] Ethyl (5α,17β)-3-oxo-4-azaandrost-1-ene-17-carboxylate.
[e] (17α)-*N*-[2,5-Bis(trifluoromethyl)phenyl]-3-oxo-4-azaandrost-1,5(6)-diene-17-carboxamide.
[f] (1α,5α,17β)-*N*-[2,5-Bis(trifluoromethyl)phenyl]-1-chloro-3-oxo-4-azaandrostane-17-carboxamide.
[g] (17β)-*N*-[2,5-Bis(trifluoromethyl)phenyl]-3-oxo-4-azaandrost-1,5(6)-diene-17-carboxamide.

• **ORGANIC IMPURITIES, PROCEDURE 2**
Diluent, System suitability solution, and **Sample solution:** Prepare as directed in the *Assay*.

Mobile phase: Acetonitrile and water (80:20)
Chromatographic system
(See *Chromatography* ⟨621⟩, *System Suitability*.)
Mode: LC
Detector: UV 220 nm
Column: 4.6-mm × 15-cm; 5-µm packing L11
Flow rate: 1 mL/min
Injection volume: 10 µL
Run time: 5 times the retention time of dutasteride
System suitability
Sample: *System suitability solution*
Suitability requirements
Resolution: NLT 1.5 between dutasteride α-dimer and dutasteride β-dimer peaks
Analysis
Sample: *Sample solution*
Integrate the dutasteride peak and all drug-related peaks eluting after the dutasteride peak.
Calculate the percentage of each impurity in the portion of Dutasteride taken:

$$\text{Result} = (r_U/r_T) \times (1/F) \times 100$$

r_U = peak area of each impurity from the *Sample solution*
r_T = sum of all the peak areas from the *Sample solution*
F = relative response factor (see *Table 4*)
Acceptance criteria: See *Table 4*.

Table 4

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
Dutasteride	1.0	—	—
Dihydrodutasteride[a]	1.19	1.0	0.15
Dutasteride α-dimer	3.7	1.0	0.3
Dutasteride β-dimer	4.3	1.0	0.5
Any other individual impurity	—	1.0	0.1
Total impurities[b]	—	—	2.0

[a] (5α,17β)-*N*-[2,5-Bis(trifluoromethyl)phenyl]-3-oxo-4-azaandrostane-17-carboxamide.
[b] Sum of impurities from *Table 3* and *Table 4*.

SPECIFIC TESTS

Change to read:

- **WATER DETERMINATION ⟨921⟩,** *Method I, Method Ic*
Sample: 100 mg
Analysis: The *Sample* is heated in a tube at 180° for 4 min in a stream of dry inert gas.
Acceptance criteria
For the anhydrous form: NMT 0.50%
For the hydrate form: NMT •2.0%. For the hydrate form, *Water Determination* ⟨921⟩, *Method I, Method Ia* may also be used.• (RB 1-Jan-2018)
- **OPTICAL ROTATION ⟨781S⟩,** *Procedures, Specific Rotation*
Sample solution: 10 mg/mL in chloroform and alcohol (98:2)
Acceptance criteria: +15.0° to +25.0°

ADDITIONAL REQUIREMENTS

- **PACKAGING AND STORAGE:** Preserve in tight containers, and store below 30°.
- **LABELING:** Where it is the hydrate form, the label so indicates.
- **USP REFERENCE STANDARDS ⟨11⟩**
USP Dutasteride RS
USP Dutasteride Resolution Mixture RS
The mixture contains Dutasteride and the following impurities (other impurities may also be present):
Dutasteride 17α-epimer: (5α,17α)-*N*-[2,5-Bis(trifluoromethyl)phenyl]-3-oxo-4-azaandrost-1-ene-17-carboxamide.
$C_{27}H_{30}F_6N_2O_2$ 528.53
Dutasteride α-dimer: {[(5α,17β)-*N*-[2,5-Bis(trifluoromethyl)phenyl]-3-oxo-4-azaandrost-1-ene-17-carboxamide-]4-yl}{[(5α,17α)-3-oxo-4-azaandrost-1-ene]-17-yl}methanone.
$C_{46}H_{55}F_6N_3O_4$ 827.94
Dutasteride β-dimer: {[(5α,17β)-*N*-[2,5-Bis(trifluoromethyl)phenyl]-3-oxo-4-azaandrost-1-ene-17-carboxamide-]4-yl}{[(5α,17β)-3-oxo-4-azaandrost-1-ene]-17-yl}methanone.
$C_{46}H_{55}F_6N_3O_4$ 827.94