Dutasteride

Type of Posting	Notice of Intent to Revise
Posting Date	29–Jul–2016; updated 01–Dec–2016[1]
Targeted Official Date	To Be Determined, Revision Bulletin
Expert Committee	Chemical Medicines Monographs 5

In accordance with section 7.04 (c) of the 2015–2020 Rules and Procedures of the Council of Experts and the Pending Monograph Guideline, this is to provide notice that the Chemical Medicines Monographs 5 Expert Committee intends to revise the Dutasteride monograph.

Comments with supporting data were received from a manufacturer that is awaiting FDA approval indicating that revisions are needed to accommodate a different polymorphic form of dutasteride. The Expert Committee proposes to revise the Dutasteride monograph as follows:

- Add chemical information for the hydrate form
- Add a second water determination test for the hydrate form
- Add a Labeling section with a requirement to label the hydrate form.

The proposed revisions are contingent on FDA approval of a product that meets the proposed monograph. The proposed revision will be published as a Revision Bulletin and an official date will be assigned to coincide as closely as possible with the FDA approval of the associated product.

See below for the proposed text.[2]

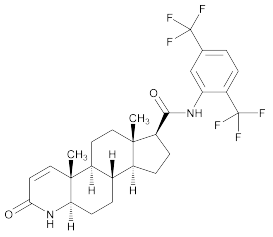
Should you have any questions, please contact Mary Koleck, Ph.D., Scientific Liaison (301-230-7420 or mpk@usp.org.) or Domenick Vicchio, Ph.D., Director of Chemical Medicines (301–998–6828 or dwv@usp.org).

[1] The proposed text was updated on December 1, 2016, to include changes related to an *Erratum* that was posted on November 18, 2016 and became official on December 1, 2016. For details on the *Erratum* that was incorporated in the proposed text please refer to the Errata table entry.

[2]This text is not the official version of a *USP–NF* monograph and may not reflect the full and accurate contents of the monograph in effect today. Please refer to the current edition of the *USP–NF* for official text.

USP provides this text as a courtesy to indicate changes that we anticipate will be made effective once the product subject to this pending monograph receives FDA approval. Once FDA approval is granted, the effective monograph will include the changes indicated herein and any changes indicated in the product's final approval, combined with the text of the monograph as effective on the date of approval.

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;

$\alpha,\alpha,\alpha,\alpha',\alpha',\alpha'$-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 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.

Change to read:

• **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● (RB 1-Jun-2016)	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.● (ERR 1-Dec-2016)
[b] Sum of impurities from *Table 3* and *Table 4*.

SPECIFIC TESTS

Delete the following:

►• **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: NMT 0.50%◄ (TBD)

Add the following:

►• **WATER DETERMINATION** ⟨**921**⟩
For the anhydrous form
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: NMT 0.50%
For the hydrate form
Sample: 100 mg
Analysis: Proceed as directed in *Water Determination* ⟨921⟩, *Method I, Method Ia*.
Acceptance criteria: NMT 2.0%◄ (TBD)
• **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°.

Add the following:

►• **LABELING:** Where it is the hydrate form, the label so indicates.◄ (TBD)
• **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