

Dutasteride

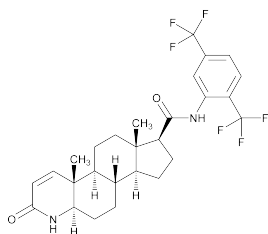
Type of Posting	Revision Bulletin
Posting Date	27–May–2016
Official Date	01–Jun–2016
Expert Committee	Chemical Medicines Monographs 5
Reason for Revision	Compliance

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 for the revision is to change the relative response factor of dihydrodutasteride from 0.38 to 1.0 to accommodate a drug substance from another FDA approved manufacturer.

The Dutasteride Revision Bulletin supersedes the Interim Revision Announcement (IRA) for Dutasteride which became official on March 1, 2016. The Revision Bulletin will be incorporated in *USP 40–NF 35*.

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

Dutasteride



$C_{27}H_{30}F_6N_2O_2$ 528.53
(5 α ,17 β)-N-[2,5-Bis(trifluoromethyl)phenyl]-3-oxo-4-azaandrost-1-ene-17-carboxamide;
 $\alpha,\alpha,\alpha,\alpha',\alpha'$ -Hexafluoro-3-oxo-4-aza-5 α -androst-1-ene-17 β -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

Change to read:

- **A. INFRARED ABSORPTION** (197K) or (197M). • (197A) may be used. • (IRA 1-Mar-2016)
- **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 \times 25-cm; 5- μ m packing L1

Column temperature: 35°

Flow rate: 1 mL/min

Injection volume: 10 μ L

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 17 α -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%

Change to read:

- **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 μ g/mL of platinum in *Diluent*. Prepare by diluting (1:100) a 1000- μ g/mL commercially available platinum standard.

Standard solution 1: 1.0 μ g/mL of platinum in *Diluent* from the *Standard stock solution*

Standard solution 2: 0.1 μ g/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 μ g/g for platinum. • (IRA 1-Mar-2016)

Calculate the limit of quantitation from the *Diluent*:

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

SD = standard deviation of platinum from *Diluent* (μ g/mL)

C_S = nominal concentration of •dutasteride • (IRA 1-Mar-2016) 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 μ g/mL) of platinum. Determine the concentration, in μ g/mL, of platinum in the *Sample solution* from the calibration curve.

Calculate the concentration, in μ g/g, of platinum in the portion of Dutasteride taken:

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

C_S = concentration of platinum in the *Sample solution* (μ g/mL)

C_U = concentration of Dutasteride in the *Sample solution* (g/mL)

2 Dutasteride

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*-heptane 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
<i>n</i> -Heptane	0.85	0.5
Pyridine	0.92	0.2
Toluene	1.0	0.2

Change to read:

• **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 17 α -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 17 α -5-ene ^e	0.90	1.0	0.2
Dutasteride 17 α -epimer	0.93	1.0	0.3
Dutasteride	1.00	—	—
Chlorodutasteride ^f	1.15	0.33	0.4

^a (5 α ,17 β)-3-Oxo-4-azaandrost-1-ene-17-carboxylic acid.

^b (5 α ,17 β)-*N,N*-Dimethyl-3-oxo-4-azaandrost-1-ene-17-carboxamide.

^c Methyl (5 α ,17 β)-3-oxo-4-azaandrost-1-ene-17-carboxylate.

^d Ethyl (5 α ,17 β)-3-oxo-4-azaandrost-1-ene-17-carboxylate.

^e (17 α)-*N*-[2,5-Bis(trifluoromethyl)phenyl]-3-oxo-4-azaandrost-1,5(6)-diene-17-carboxamide.

^f (1 α ,5 α ,17 β)-*N*-[2,5-Bis(trifluoromethyl)phenyl]-1-chloro-3-oxo-4-azaandrostane-17-carboxamide.

^g (17 β)-*N*-[2,5-Bis(trifluoromethyl)phenyl]-3-oxo-4-azaandrost-1,5(6)-diene-17-carboxamide.

• **Table 3** (Continued)

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
Dutasteride 5-enes	1.20	1.0	0.3
Any other individual impurity	—	—	0.1

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

• (IRA 1-Mar-2016)

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 \times 15-cm; 5- μ m packing L11

Flow rate: 1 mL/min

Injection volume: 10 μ L

Run time: 5 times the retention time of dutasteride

System suitability

Sample: System suitability solution

Suitability requirements

Resolution: NLT \bullet 1.5 \bullet (IRA 1-Mar-2016) 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:

\bullet Result = $(r_U/r_T) \times (1/F) \times 100$ (IRA 1-Mar-2016)

r_U = peak area of each impurity from the Sample solution

r_T = sum of all the peak areas from the Sample solution

\bullet F = relative response factor (see Table 4) \bullet (IRA 1-Mar-2016)

Acceptance criteria: See Table 4.

• **Table 4**

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
Dutasteride	1.0	—	—
Dihydrodutasteride ^a	1.19	\bullet 1.0 \bullet (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 (5 α ,17 β)-N-[2,5-Bis(trifluoromethyl)phenyl]-3-oxo-4-azaandrost-17-carboxamide.

^b Sum of impurities from Table 3 and Table 4.

• (IRA 1-Mar-2016)

SPECIFIC TESTS

Change to read:

• **WATER DETERMINATION** <921>, Method I, Method Ic

Sample: 100 mg

Analysis: \bullet The Sample is heated in a tube at 180 $^\circ$ for 4 min in a stream of dry inert gas. \bullet (IRA 1-Mar-2016)

Acceptance criteria: NMT 0.50%

• **OPTICAL ROTATION** <781S>, Procedures, Specific Rotation

Sample solution: 10 mg/mL in chloroform and alcohol (98:2)

Acceptance criteria: +15.0 $^\circ$ to +25.0 $^\circ$

ADDITIONAL REQUIREMENTS

• **PACKAGING AND STORAGE:** Preserve in tight containers, and store below 30 $^\circ$.

Change to read:

• **USP REFERENCE STANDARDS** <11>

USP Dutasteride RS

USP Dutasteride Resolution Mixture RS

The mixture contains \bullet Dutasteride and \bullet (IRA 1-Mar-2016) the following impurities (other impurities may also be present):

Dutasteride 17 α -epimer: (5 α ,17 α)-N-[2,5-Bis(trifluoromethyl)phenyl]-3-oxo-4-azaandrost-1-ene-17-carboxamide.

C₂₇H₃₀F₆N₂O₂ 528.53

Dutasteride α -dimer: {[(5 α ,17 β)-N-[2,5-Bis(trifluoromethyl)phenyl]-3-oxo-4-azaandrost-1-ene-17-carboxamide-]4-yl}{[(5 α ,17 α)-3-oxo-4-azaandrost-1-ene]-17-yl}methanone.

C₄₆H₅₅F₆N₃O₄ 827.94

Dutasteride β -dimer: {[(5 α ,17 β)-N-[2,5-Bis(trifluoromethyl)phenyl]-3-oxo-4-azaandrost-1-ene-17-carboxamide-]4-yl}{[(5 α ,17 β)-3-oxo-4-azaandrost-1-ene]-17-yl}methanone.

C₄₆H₅₅F₆N₃O₄ 827.94