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Dutasteride Capsules

Details for the public consultation of this monograph are as follows:

EAG/Panel/Working Party	Medicinal Chemicals 3
Contact Details	adrian.evans@mhra.gov.uk
Deadline for Comment	31st March 2019
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Notes:	New monograph If limits are too restrictive, please provide batch/stability data to demonstrate that an increase is required. **Comments on the usability on the EPCRS in the Assay/Related substances would be welcomed**

Action and use

5-Alpha reductase inhibitor; treatment of benign prostatic hyperplasia.

DEFINITION

Dutasteride Capsules contain Dutasteride.

The Capsules comply with the requirements stated under Capsules and with the following requirements.

Content of dutasteride, $C_{27}H_{30}F_6N_2O_2$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. In the test for Related substances, the chromatogram obtained with solution (1) shows a peak with the same retention time as the principal peak in the chromatogram obtained with solution (4).
B. In the test for Uniformity of Content, the chromatogram obtained with solution (1) shows a peak with the same retention time as the principal peak in the chromatogram obtained with solution (2).

TESTS

Dissolution

Comply with the dissolution test for tablets and capsules, Appendix XII B1.

TEST CONDITIONS

(a) Use Apparatus 2, rotating the paddle at 50 revolutions per minute.
(b) 450 mL of 0.1M hydrochloric acid with 0.16% w/v pepsin for the first 25 minutes, followed by addition of 450 mL of 0.1M hydrochloric acid with 4% w/v sodium dodecyl sulfate for the remainder of the dissolution test.

PROCEDURE

Carry out the method for liquid chromatography, Appendix III D, using the following solutions.

(1) After 45 minutes withdraw a sample of the medium and filter. Dilute the filtrate, if necessary, with a 2% w/v solution of sodium dodecyl sulfate in 0.1M hydrochloric acid to produce a solution expected to contain 0.00005% w/v of Dutasteride.
(2) 0.00005% w/v of dutasteride EPCRS in 2% w/v solution of sodium dodecyl sulfate in 0.1M hydrochloric acid.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (15 cm × 3 mm) packed with phenylsilyl silica gel for chromatography (3.5 µm) (Zorbax SB-Phenyl is suitable).
(b) Use isocratic elution and the mobile phase described below.
(c) Use a flow rate of 0.5 mL per minute.
(d) Use a column temperature of 37°.
(e) Use a detection wavelength of 240 nm.
(f) Inject 50 µL of each solution.

MOBILE PHASE

55 volumes of acetonitrile and 45 volumes of water.

DETERMINATION OF CONTENT

Calculate the total content of $C_{27}H_{30}F_6N_2O_2$, in the medium from the chromatograms obtained and using the declared content of $C_{27}H_{30}F_6N_2O_2$ in dutasteride EPCRS.

LIMITS

The amount of $C_{27}H_{30}F_6N_2O_2$ released is not less than 80% (Q) of the stated amount.

Related substances

Carry out the method for liquid chromatography, Appendix III D, using the following solutions.

(1) Transfer 5 capsules into a 250 mL volumetric flask, add 50 mL of the mobile phase and cut the capsules, taking care to rinse the cutting tool with the mobile phase. Dilute with a sufficient quantity of the mobile phase to produce a solution containing 0.001% w/v of Dutasteride.
(2) Dilute 1 mL of solution (1) to 100 mL with the mobile phase.
(3) Dilute 10 mL of solution (2) to 100 mL with the mobile phase.
(4) Dissolve 0.001% w/v of dutasteride EPCRS in the mobile phase.
(5) Dissolve 12.5 mg of dutasteride for system suitability EPCRS in 10 mL of the mobile phase.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with cyanosilyl silica gel for chromatography (5µm) (Zorbax SB-CN is suitable).
(b) Use isocratic elution and the mobile phase described below.
(c) Use a flow rate of 1 mL per minute.

(d) Use an ambient column temperature.
(e) Use a detection wavelength of 240 nm.
(f) Inject 50 µL of each solution.
(g) For solution 1 allow to run for twice the retention time of dutasteride.

MOBILE PHASE

90 volumes of hexane and 10 volumes of isopropanol.

When the chromatograms are recorded under the prescribed conditions, the relative retention with reference to dutasteride (retention time, about 26 min) is about 1.1.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (5), the resolution between the peaks due to impurity E and dutasteride is at least 1.5.

LIMITS

In the chromatogram obtained with solution [(1)]:

the area of any *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (1%);

the sum of the areas of all *secondary peaks* is not greater than twice the area of the principal peak in the chromatogram obtained with solution (2) (2%).

Disregard any peak with an area less than the area of the principal peak in the chromatogram obtained with solution (3) (0.1%).

Uniformity of content

Carry out the method for liquid chromatography, Appendix III D, using the following solutions.

Solution A 60 volumes of water and 40 volumes of acetonitrile
(1) Transfer 1 capsule to a 50 mL volumetric flask, add 10 mL of solution A and cut the capsule, taking care to rinse the cutting tool with solvent A. Add sufficient solution A to produce a solution containing 0.001% w/v of Dutasteride, allow to stand at room temperature for 30 minutes, shake with the aid of ultrasound for 30 minutes and filter.
(2) 0.001% w/v of dutasteride EPCRS in solvent A.
(3) To 10 volumes of a 0.01% w/v solution of dutasteride EPCRS in solution A, add 10 volumes of a 0.07% w/v solution of butylated hydroxytoluene in methanol and dilute to 100 volumes with solution A.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (5 cm × 3 mm) packed with base-deactivated octadecylsilyl silica gel for chromatography (1.8 µm) (Zorbax SB-C18 is suitable).
(b) Use gradient elution and the mobile phase described below.
(c) Use a flow rate of 1.5 mL per minute.
(d) Use a column temperature of 60°.
(e) Use a detection wavelength of 280 nm.
(f) Inject 50 µL of each solution.

MOBILE PHASE

Mobile phase A 0.1% v/v trifluoroacetic acid in water.

Mobile phase B 0.1% v/v trifluoroacetic acid in acetonitrile.

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0-4	48	52	isocratic
4-5	48→10	52→90	linear gradient
5-6	10	90	isocratic
6-7	10→48	90→52	linear gradient
7-12	48	52	re-equilibration

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the resolution between the peaks due to dutasteride and butylated hydroxytoluene is at least 1.5.

DETERMINATION OF CONTENT

Calculate the total content of $C_{27}H_{30}F_6N_2O_2$, in the capsules from the chromatograms obtained and using the declared content of $C_{27}H_{30}F_6N_2O_2$ in dutasteride EPCRS.

ASSAY

Use the average of the individual results determined in the test for Uniformity of content.

IMPURITIES

The impurities limited by the requirements of this monograph include those listed under *Dutasteride*.