Edition: BP 2025 (Ph. Eur. 11.6 update)

Tibolone Tablets

General Notices

DEFINITION

Tibolone Tablets contain Tibolone.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of tibolone, $C_{21}H_{28}O_2$

90.0 to 105.0% of the stated amount.

IDENTIFICATION

A. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.
(1) Shake a quantity of the powdered tablets containing 5 mg of Tibolone with 5 mL of *acetonitrile*, centrifuge and use the supernatant liquid.
(2) 0.1% w/v of *tibolone BPCRS* in *acetonitrile*.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel G* (Merck silica gel 60 plates are suitable).
(b) Use the mobile phase described below.
(c) Apply 4 µL of each solution.
(d) Develop the plate to 15 cm.
(e) After removal of the plate dry in air, spray with *ethanolic sulfuric acid (2%)* and heat at 100° to 105° for 3 minutes. Allow to cool and examine under *ultraviolet light (366 nm)* and in daylight.

MOBILE PHASE

5 volumes of *acetone* and 95 volumes of *dichloromethane*.

CONFIRMATION

The principal spot in the chromatogram obtained with solution (1) is similar in position, colour and size to that in the chromatogram obtained with solution (2).

B. In the test for Uniformity of content, the chromatogram obtained with solution (1) exhibits a peak with the same retention time as the peak due to tibolone in the chromatogram obtained with solution (2).

TESTS

Dissolution

Comply with the requirements in 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) Use 500 mL of a 0.25% w/v solution of *sodium lauryl sulfate*, at a temperature of 37°, as the medium.

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. Use the filtered medium, diluted with a 0.25% w/v solution of *sodium lauryl sulfate* to produce a solution expected to contain about 0.0005% w/v of Tibolone.
(2) 0.0005% w/v of *tibolone BPCRS* in a mixture of 1 volume of *methanol* and 99 volumes of a 0.25% w/v solution of *sodium lauryl sulfate*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (10 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Hypersil ODS 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 40°.
(e) Use a detection wavelength of 205 nm.
(f) Inject 200 µL of each solution.

MOBILE PHASE

23 volumes of *water* and 77 volumes of *methanol R2*.

DETERMINATION OF CONTENT

Calculate the total content of tibolone, $C_{21}H_{28}O_2$, in the medium from the chromatograms obtained and using the declared content of $C_{21}H_{28}O_2$ in *tibolone BPCRS*.

LIMITS

The amount of tibolone released is not less than 75% (Q) of the stated amount.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in *absolute ethanol*.

(1) To a quantity of the powdered tablets containing 25 mg of Tibolone add 40 mL of *absolute ethanol*, mix with the aid of ultrasound, add sufficient *absolute ethanol* to produce 50 mL, centrifuge and use the supernatant.
(2) 0.05% w/v of *tibolone impurity standard BPCRS* (containing impurity B, impurity C and 1% w/w of impurity A).
(3) Dilute 1 volume of solution (2) to 10 volumes.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (15 cm × 3.9 mm) packed with *octadecylsilyl silica gel for chromatography* (4 µm) (Waters Nova-Pak C18 is suitable).
(b) Use isocratic elution and the mobile phase described below.
(c) Use a flow rate of 1 mL per minute.
(d) Use a column temperature of 40°.
(e) Use a detection wavelength of 240 nm.
(f) Inject 10 µL of each solution.

MOBILE PHASE

28 volumes of *tetrahydrofuran* and 72 volumes of *water*.

SYSTEM SUITABILITY

The test is not valid unless:

the chromatogram obtained with solution (2) closely resembles the chromatogram supplied with *tibolone impurity standard BPCRS*;

in the chromatogram obtained with solution (2), the *resolution* between the peaks due to impurity A and impurity B is at least 2.0;

in the chromatogram obtained with solution (3), the *signal-to-noise* ratio of the peak due to impurity A is at least 10.

LIMITS

Identify any peak in the chromatogram obtained with solution (1) corresponding to impurity C using the chromatogram obtained with solution (2) and multiply the area of this peak by the following correction factor: 0.79.

In the chromatogram obtained with solution (1):

the area of any peak corresponding to impurity A is not greater than the area of the corresponding peak in the chromatogram obtained with solution (2) (1%);

the area of any peak corresponding to impurity B is not greater than the area of the peak due to impurity A in the chromatogram obtained with solution (2) (1%);

the area of any peak corresponding to impurity C is not greater than 5 times the area of the peak due to impurity A in the chromatogram obtained with solution (2) (5%);

the area of any other *secondary peak* is not greater than 0.5 times the area of the peak due to impurity A in the chromatogram obtained with solution (2) (0.5%);

the sum of the areas of all the *secondary peaks* is not greater than 6.5 times the area of the peak due to impurity A in the chromatogram obtained with solution (2) (6.5%).

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

Uniformity of content

For tablets containing 2 mg or less or 2% w/w or less of tibolone

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in *absolute ethanol*.

(1) Finely crush one tablet, moisten the powdered tablet with sufficient *absolute ethanol* to produce a solution containing 0.05% w/v of Tibolone, disperse with the aid of ultrasound for 10 minutes and centrifuge.
(2) 0.05% w/v of *tibolone BPCRS*.
(3) 0.05% w/v of *tibolone impurity standard BPCRS*.

CHROMATOGRAPHIC CONDITIONS

The chromatographic procedure described under Related substances may be used with a detection wavelength of 210 nm.

SYSTEM SUITABILITY

The test is not valid unless:

the chromatogram obtained with solution (3) closely resembles the chromatogram supplied with *tibolone impurity standard BPCRS*;

in the chromatogram obtained with solution (3), the *resolution* between the peaks due to impurity A and impurity B is at least 2.0.

DETERMINATION OF CONTENT

Calculate the content of $C_{21}H_{28}O_2$ in each tablet using the declared content of $C_{21}H_{28}O_2$ in *tibolone BPCRS*.

ASSAY

For tablets containing 2 mg or less or 2% w/w or less of tibolone

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

For tablets containing more than 2 mg and more than 2% w/w of tibolone

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in *absolute ethanol*.

(1) To a quantity of the powdered tablets containing 25 mg of Tibolone add 40 mL of *absolute ethanol*, mix with the aid of ultrasound, add sufficient *absolute ethanol* to produce 50 mL and centrifuge.
(2) 0.05% w/v of *tibolone BPCRS*.
(3) 0.05% w/v of *tibolone impurity standard BPCRS*.

CHROMATOGRAPHIC CONDITIONS

The chromatographic procedure described under Related substances may be used with a detection wavelength of 210 nm.

SYSTEM SUITABILITY

The test is not valid unless:

the chromatogram obtained with solution (3) closely resembles the chromatogram supplied with *tibolone impurity standard BPCRS*;

in the chromatogram obtained with solution (3), the *resolution* between the peaks due to impurity A and impurity B is at least 2.0.

DETERMINATION OF CONTENT

Calculate the content of $C_{21}H_{28}O_2$ in the tablets using the declared content of $C_{21}H_{28}O_2$ in *tibolone BPCRS*.

IMPURITIES

A. 10,17-dihydroxy-7α-methyl-19-nor-10ξ,17α-pregn-4-en-20-yn-3-one (European Pharmacopoeia impurity A),
B. 10-hydroperoxy-17-hydroxy-7α-methyl-19-nor-10ξ,17α-pregn-4-en-20-yn-3-one (European Pharmacopoeia impurity B),
C. 17-hydroxy-7α-methyl-19-nor-10ξ,17α-pregn-4-en-20-yn-3-one (European Pharmacopoeia impurity C).